American Journal of Obstetrics and Gynecology

VOL. 66 DECEMBER, 1953 NO. 6

Transactions of the Texas Association of Obstetricians and Gynecologists

INFLUENCE OF WEIGHT GAIN ON PREGNANCY*

A Review of One Thousand Private Cases

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THIS study was undertaken to determine what effect, if any, weight gain has on pregnancy and labor, and to ascertain what constitutes a normal weight gain during pregnancy.

Loughran,[1] in a report on 352 patients, in whom weight gain was restricted to 15 to 20 pounds, showed a decrease in the length of labor, lessened incidence of dystocia, and an absence of toxemia.

Luikart[2] reported on 1,000 patients with normal initial weights who were organically sound when first seen. Weight gain was restricted to 16 pounds or less and to a maximum of 2 pounds in any one month. He had no maternal deaths, no cases of toxemia, and a fetal mortality of only 0.6 per cent.

Dieckmann[3] states, "Every patient whose total weight gain is over 10.9 kilograms does not necessarily have toxemia. Statistics do show, however, that the incidence of toxemia is increased in those patients who gain more than 13 kilograms." Dieckmann[4] also reports that the average gain in normal pregnancy is 10.1 kilograms. In his clinic the incidence of toxemia is 7.4 per cent; 54 per cent of the pre-eclamptic group and 34 per cent of the hypertensive group gained over 10 kilograms. The rate of gain in weight rather than the total amount of weight gain seemed to be of first importance.

Dawson and Borg[5] found that in 93 toxemic women with 863 pregnancies reported, the weight gain during the whole gestational period was from 12 to 29 per cent greater than the average gain. This he found to be 24.85 pounds.

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Fort Worth, Feb. 13-14, 1953.

In a series of 521 deliveries of obese women, all of whom weighed over 200 pounds, Douglas and Scadron[6] found that obesity per se apparently mattered very little. They found no increase in prolonged labor, no increase in abnormal presentations, nor was fetal or maternal mortality increased. However, in the antepartum period, one patient in five showed some elevation in blood pressure and 55 patients had specific hypertensive disease of pregnancy. Many of the dangers faced by these obese women in childbearing were directly or indirectly due to excessive fetal size, particularly shoulder dystocia. Even so, they had only 12 sections for disproportion.

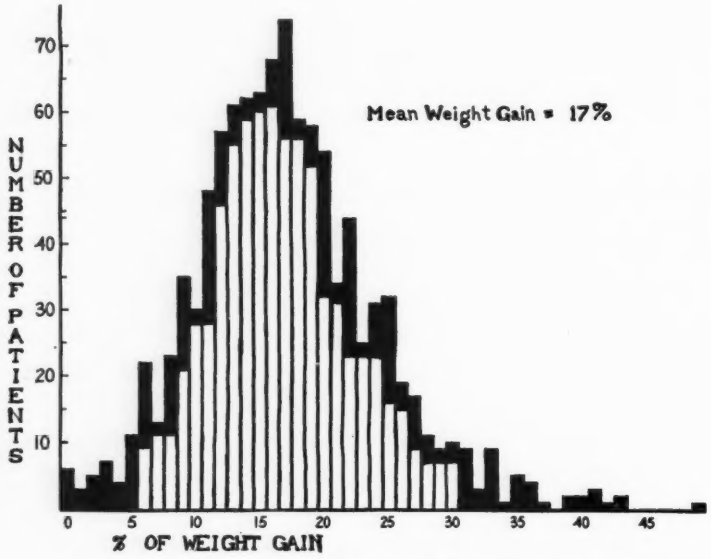

Fig. 1.—Incidence of weight gain by percentage increase.

Tompkins and Wiehl[7] in a study of 760 cases showed that patients who were overweight at the onset of pregnancy, or who gained excessively, had an increased incidence of toxemia. This was particularly true where the rate of gain in the first two trimesters was greater than the average rate of the group. If the excessive rate of gain continued into the third trimester, the toxemia incidence was even more marked, whereas, if the rate in the third trimester fell to less than that of the group as a whole, the tendency toward toxemia decreased.

Paradoxically, in a group markedly underweight at the beginning of pregnancy, there was twice the incidence of toxemia as in that group who were greatly overweight at the start of their pregnancies. The underweight group also showed a higher incidence of premature labor; this incidence was lowered in a comparable series who took nutritional supplements, namely, protein and vitamins.

As regards an average or normal weight gain in pregnancy, three standard texts on obstetrics list this as 24 pounds, 23.2 pounds, and between 20 and 25 pounds.

Materials and Methods

In our study, 1,000 cases, unselected, were reviewed. All records were from our private patients, the majority of whom would be described as being in the middle income group. No attempt was made to determine minutely caloric intakes or personal idiosyncrasies in dietary habits. However, a basic diet suggested was high in protein, particularly meat, eggs, and milk. To this were added starches and fats depending on patient desires and the rate of weight gain. Salt was restricted or eliminated according to weight gain and edema formation. In the event of an excessive or a too rapid gain in weight most patients were put on sharply restricted diets. These were never less than 1,000 calories daily and an adequate protein intake was insisted upon. Markedly restricted diets were never continued longer than was absolutely necessary. All patients were routinely given some form of iron and vitamin supplement; calcium, as such, we feel is largely wasted medication.

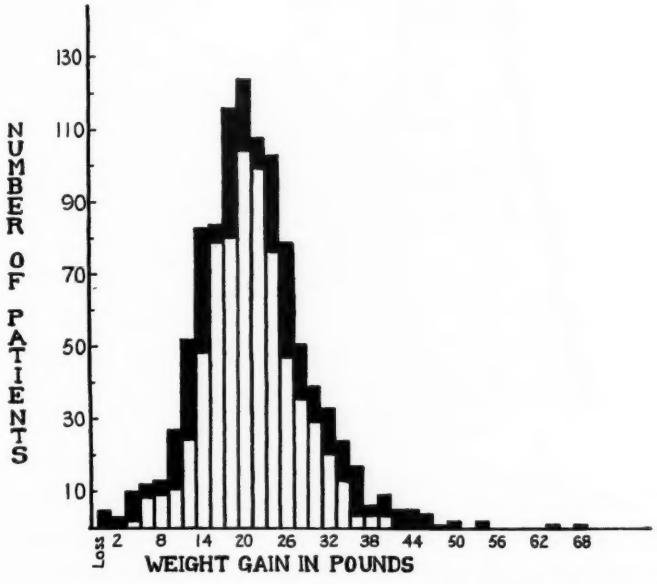

Fig. 2.—Incidence of weight gain by increase in pounds.

In labor, no routine was practiced. However, sedation for the most part consisted of Demerol and hyoscine, with or without the addition of barbiturates. Anesthesia was mostly gas and/or ether. Rarely local infiltration or pudendal block was used. In premature labors, little or no sedation was given and low spinal anesthesia, usually Pontocaine, was utilized if at all feasible. Spinal anesthesia was virtually routine for cesarean section.

Results

The mean percentage weight gain in our series was 17 per cent of initial body weight. The extremes varied from 0 to 49 per cent, as will be noted in Fig. 1. The weight gain in pounds varied from 3 pounds in 3 patients to 69 pounds in 1 patient. Over half (615) patients gained between 14 and 24 pounds, the largest number (128) gaining 20 pounds. These data are shown in Fig. 2.

The ages of the patients varied from a low of 14 years to a high of 44 years, with a mean age of 26.5 years as shown in Fig. 3.

Patients over 26 years of age had a tendency to gain less than the 17 per cent median gain whereas in the 15 to 26 year group the number gaining less than the median is almost identical with that gaining more. These findings are shown in Fig. 4.

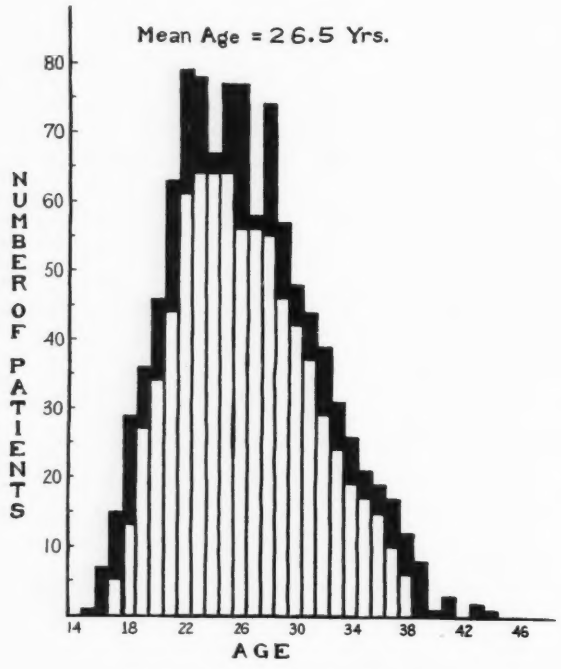

Fig. 3.—Distribution of patients by age.

Fig. 5 shows that of 362 patients with a weight gain greater than the average, 84 had labor lasting longer than eight hours, and 278 had labors of less than eight hours' duration. In the 614 patients with less than the average gain, 110 had labors lasting more than eight hours, 504 had labors shorter than eight hours in duration. This seems to indicate that excess weight gain invites longer labor. However, since the median length of labor in our series was only seven hours, we do not feel that statistically this finding is significant.

Table I shows our findings in regard to toxemia. The total number of cases is 30, giving an incidence of 3 per cent. This is about half the usual reported incidence. In the toxemia patients, the average weight gain was 22.4 per cent, as contrasted to 17 per cent for the series as a whole. The weight gain varied from 6 to 40 per cent of body weight and from 8 to 41 pounds. The length of labor was 7.3 hours as against 7 hours for the entire series. The age difference was not significant—25.5 years for toxemic patients and 26.5 for the group as a whole. About two-thirds of the cases of toxemia were in primiparas.

Comment

From our study it appears that 17 per cent of the body weight or 20 to 25 pounds is a normal gain during pregnancy. This agrees with other reports in the literature. Restriction of weight gain to 15 pounds therefore would have little merit; conversely, 25 pounds gained throughout gestation should occasion little alarm. While our figures show that all our patients

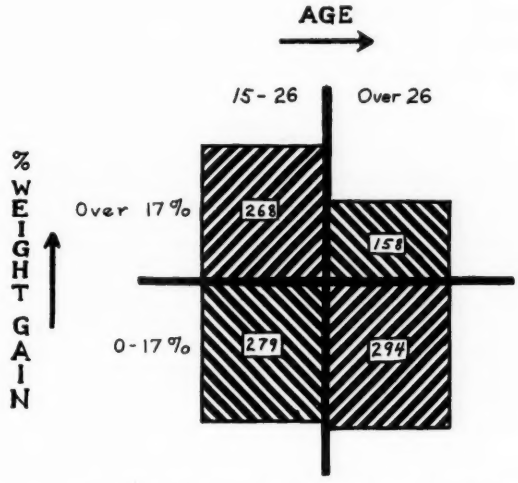

Fig. 4.—The relation of age and weight gain.

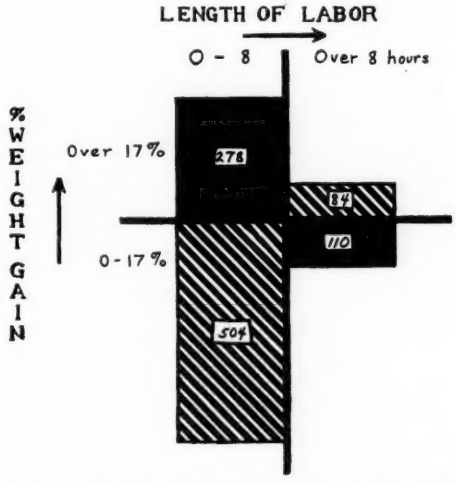

Fig. 5.—Relation of length of labor and weight gain.

with toxemia had a greater-than-average gain, by far the great majority with excess weight gain did not develop toxemia. This is somewhat in conflict with the reports of others. Our number of cases of toxemia is admittedly small and we have no breakdown as to the edema weight and weight due to eating habits alone. This may be of some significance.

In our series, patients 25 years and older showed less of a tendency toward excess weight gain. This probably can be explained on the basis of better cooperation and intelligence of the mature individual. Weight gain per se apparently plays very little part in the duration of labor. Our absolute figures tend to show the opposite to be true; however, when the average duration of labor for a whole group is considered, statistically, in our series at least, there is no significance.

TABLE I. STATISTICS OF TOXEMA, THIRTY CASES

	TOXEMIA	EXPECTED	SIGNIFICANCE
Weight gain	22.4%	17%	Yes (1% level)
Length of labor	7.3 hours	7 hours	No
Age	25.5 years	26.5 years	No
Gravidity			
Primiparas	63%	41%	Yes
Secundiparas	23%	37%	Yes
Two+	13%	21%	Yes
Weight range in toxemia cases			
	8 pounds—41 pounds		
	6% —40%		

Summary

1. A review of 1,000 cases, analyzed from the standpoint of weight gain during pregnancy, is reported.

2. A normal weight gain during pregnancy is 20 to 25 pounds or 17 per cent of body weight.

3. The degree of weight gain has no influence on the length of labor.

4. Weight gain per se has very little, if any influence on the development of toxemia.

TABLE II. STATISTICAL SUMMARY

	NUMBER	WEIGHT GAIN	SIGNIFICANCE
Gravidity.—			
i	414	17.6%	
ii	371	17.0%	
ii+	215	16.8%	Tendency to gain less
Toxemias.—	30	22.3%	Significant to 1% level
Length of Labor.—			
0 to 8 hours	504	0 - 17%	
0 to 8 hours	270	18%+	No relation
9+ hours	112	0 - 17%	
9+ hours	84	18%+	
Age.—			
14 to 26 years	279	0 - 17%	----
14 to 26 years	268	18%+	----
27 years+	294	0 - 17%	----
27 years+	158	18%+	Tendency to gain less

References

1. Loughran, Charles H.: AM. J. OBST. & GYNEC. 52: 42, 1946.
2. Luikart, Ralph: AM. J. OBST. & GYNEC. 52: 428, 1946.
3. Dieckmann, W. J., Turner, Dorothea F., and Ruby, Barbara A.: AM. J. OBST. & GYNEC. 50: 701, 1945.

4. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Company, pp. 284-285.
5. Dawson, Sir Bernard, and Borg, Helen: New Zealand M. J. 48: 375, 1947.
6. Douglas, Gordon W., and Scadron, Eugene N.: M. Clin. North America 35: 733, 1951.
7. Tompkins, Winslow T., and Wiehl, Dorothy C.: AM. J. OBST. & GYNEC. 62: 898, 1951.

Discussion

DR. NOEL R. BAILEY.—Drs. Alexander and Downs have very capably brought us a reiteration of some established principles of prenatal care and added some new attitudes regarding weight gain during pregnancy.

The authors' use of weight gain in percentage of body weight surely reflects a more scientific expression than the customary 20 to 25 pounds. It seems evident that 20 to 25 pounds gain during pregnancy would have a much greater effect on the diminutive patient than on the pregnant Amazon.

Even though the figures on the relationship between above average weight gain and the incidence of toxemia are reported as being equivocal and the paucity of toxic patients substantiates this, the fact is mentioned that *all* patients who developed toxemia had a greater-than-average gain. Excessive weight gain in the last trimester was present in all toxemic cases, which emphasized the importance of *alert* prenatal care during this time.

Even though the effect of weight gain on the length of labor was not marked, the essayists report an incidence of longer-than-average labor in approximately one of five in the group showing less-than-average weight gain, while one of three had longer-than-average labor of those who had greater-than-average weight gain.

It is generally agreed that pregnancy is an added responsibility on practically every organ and structure of the body and demands greater functional effort of every component part of the body. Obesity calls for a greater body response, which in many respects is similar to pregnancy. To add excessive weight gain to pregnancy might be analogous to a marathon race. It is obvious that the normally nourished contestant excels far beyond the obese or malnourished individual.

ALLERGY—A FACTOR IN ABORTIONS?*

Report on Two Cases

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SINCE the beginning of modern obstetrics, many causes for abortions have been set forth and many forms of treatment tried and gradually discarded. The exact cause of abortions has not yet been established, although empirical treatment has increased the salvage of living infants. Karnaky,[1] Smith, Smith, and Horwitz,[2] Rosenblum and Melinkoff[3] have advocated the use of diethylstilbestrol for threatened and habitual abortion with increase in salvage rate. Bartholomew[4] states that failure of normal development of the ovum is the most common cause of abortion before the end of the third month.

Hofbauer,[5] in 1926, after studies on pregnant guinea pigs, whose placentation exhibits reasonable likeness to human placental attachment, first postulated that histamine metabolism might be the cause of abortion and abruptio placentae in pregnant women. He was able to produce all variations, from partial separation of the placenta to severe abruptio with bleeding through the uterine wall extending into the broad ligament. He showed that the maternal vessels were greatly dilated and that the syncytial buds were torn or broken off. Dilatation of veins and capillaries throughout the entire generative tract was noted. Observing the pregnant uterus as the histamine was injected, he noted a marked contraction of the uterus with marked dilatation of the uterine vessels, and engorgement of the vessels in the broad ligament. In the cat with a second injection of histamine, purplish areas were noted at the ends of several segments of the uterine horns. These areas on section showed hemorrhage into the uterine muscle.

Barsoum and Gaddum,[6] in 1935, showed that histamine was a normal constituent of human blood. Morcou and Atanasi-Vergu,[7] in 1937, Giudici,[9] 1931, Effekemann and Werle,[8] 1940, reported studies of histamine levels in pregnant women but their results varied so much that they were of little value.

Marcou and associates,[10] 1938, reported that the blood of pregnant women was highly histaminolytic. Ahlmark,[11] 1944, showed that histaminase became present at about the seventh week after the first day of the last period and rapidly increased until it was 500 to 1,000 times as great by the end of the pregnancy. Danforth,[12] in 1937, showed that histaminase was a normal constituent of the human placenta.

Kapeller-Adler,[13] in 1949, in an attempt to clarify histamine metabolism in pregnant and nonpregnant women, made a study on 8 nonpregnant and 91

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Austin, Feb. 14-16, 1952.

pregnant women. In the nonpregnant women she demonstrated histamine in the blood cells of all ranging from 20 to 50 micrograms per liter of blood, a trace in 2, and 10 micrograms in one and 15 micrograms in the plasma. No histaminase was found in any of the nonpregnant women. In 25 pregnant women who showed no abnormalities there was a noted increase in the histamine in the blood cell but only a trace was found in the plasma. There was a definite amount of histaminase in all of these patients varying in amount with the duration of the pregnancy.

In mild pre-eclampsia the histaminase activity was definitely diminished; however, the plasma histamine content was definitely increased in 12 of 16 patients studied. The 4 showing only a trace had the highest histaminase activity.

The histaminase activity in moderate to severe pre-eclampsia was definitely lowered, as was the histamine content of the blood cells, while the histamine content of the plasma was greatly increased.

In 4 cases of threatened abortion the histaminase content of the blood was hardly detectable and the histamine content of the plasma was greatly increased. Histaminase quickly disappears from the blood after delivery. The above determinations were apparently single determinations during the pregnancy. Kapeller-Adler[14] has also shown that estrogen helps increase the activity of histaminase. We may find this to be the reason for the effectiveness of stilbestrol.

McElin and Horton,[15] in 1949, reported a study of 15 women treated with histamine during pregnancy who showed no untoward effects. The largest dose given was 2.75 mg. of histamine base. Ahlmark showed that pregnant women were able to destroy up to 100 micrograms of histamine an hour and stated that it might be even more.

Javert and Finn[16] made a thorough pathological study of 500 abortions. Serological and Rh factors were of the same percentage as found in the population as a whole so were not considered a contributing factor. Decidual bleeding and placental separation were found to be the most common factors and were found to be a cause and not a secondary result.

Case Reports

CASE 1.—To Dr. A. J. P. S. is due much credit for the investigation of this subject and for her cooperation in carrying out experimentation during her last pregnancy. She had had four previous pregnancies without a living child.

The first pregnancy in 1943 ended in spontaneouus abortion at 8 weeks. In the second pregnancy, 1948, cramping and bleeding began at 14 weeks. She was placed on 2 Gm. stilbestrol daily for 48 hours, then on a maintenance dose of 25 mg. three times a day. She aborted at 21 weeks. Retroplacental hemorrhage was noted. In the third pregnancy, April, 1949, she aborted at 18 weeks. She was taking 100 mg. vitamin E, high vitamin C, and 100 mg. stilbestrol daily. She aborted the fourth pregnancy, August, 1949, at 9 weeks. No fetal structures were found.

Fifth and present pregnancy: The last menstrual period was Dec. 1, 1949. She had been on a high-protein diet, 100 mg. vitamin E, and 1 grain thyroid daily for 8 months. At 8 weeks she was started on 50 mg. stilbestrol and 20 mg. progesterone daily. She spotted on March 2, 1950. This subsided on 1 Gm. stilbestrol daily and she was then placed on a

maintenance dose of 100 mg. daily. In mid-April she developed a cold which did not subside as expected, was skin tested, and found to be allergic to pecan pollen which was prevalent at that time. She took a first desensitizing dose of antigen and in about 15 minutes developed severe urticaria and sneezing. Her husband, who is also a physician, prepared to give her some antihistamine. As he was filling the syringe she began having severe uterine cramps. He gave her the antihistamine intravenously to relieve the urticaria and to his surprise the uterine cramps stopped during the injection. He called me and we decided to try more antihistamine therapy. She was placed on 50 mg. of antihistamine every 4 hours which controlled the allergy and cramps as long as therapy was taken regularly. Various antihistamines were used, depending on samples he had available. All gave equal results.

We then decided to see if an air-conditioned room would relieve hay fever and to see if uterine cramps would develop without antihistamines. She stayed in a hotel for two weeks during which time she had no hay fever or uterine cramps. Forty-eight hours after she left the hotel, uterine cramps returned with bleeding. She was given ¼ grain morphine intravenously without relief. Fifty mg. Bendadryl intravenously stopped the cramps within 10 minutes. Continued use of antihistamines was the only way the cramps could be controlled; even ½ grain morphine would not stop cramps or bleeding when she stopped the antihistamine intake for too long a period.

When the patient was 30 weeks pregnant she decided to stop taking antihistamines because of the reports in the literature of blood dyscrasias from their use. Twelve hours after taking the last dose she began having regular contractions which were not controlled by ½ grain morphine intravenously. She delivered a 3 pound, 5 ounce female infant who survived. The placenta was thrown out before it could be studied.

CASE 2.—Mrs. A. H. was seen with her first pregnancy in October, 1948. The last menstrual period was August 19. With severe nausea and vomiting and threatened abortion, she was controlled with difficulty. She continued to have attacks of cramping and bleeding. A premature infant was delivered at 22 weeks, that breathed irregularly for 20 minutes. The second pregnancy, beginning in August, 1949, followed a course similar to that of the first pregnancy, and she aborted at 20 weeks.

Third pregnancy: The last menstrual period was Oct. 25, 1950. She began having nausea and vomiting Jan. 11, 1951. This was controlled slightly with high B complex intravenously and a high-protein diet. On Jan. 18, 1950, cramping and bleeding began. She was given intravenous Bendadryl and the cramping stopped within 15 minutes; the bleeding had stopped in 24 hours. She was placed on 50 mg. Pyribenzamine every 6 hours. Nausea and vomiting were also controlled. The patient stopped medication after two weeks of her own accord and all symptoms recurred. She was placed on a maintenance dose of 50 mg. Pyribenzamine every six hours which she took until the thirty-eighth week. Forty-eight hours after the last dose of antihistamine, she went into active labor and delivered a living female infant that weighed 6 pounds, 1 ounce. Examination of the placenta showed a small, well-organized blood clot under the margin of the placenta in one area.

Summary and Conclusions

A brief review of the literature on histamine metabolism in pregnant women has been given. Experimental studies on the action of histamine on the uterus of pregnant guinea pigs have been described. A report has been made of two cases in which allergy or the action of histamine was the precipitating factor in threatened abortion, which were controlled by use of antihistamine and living children were delivered. It is well understood that these two cases are not sufficient to be of great value, especially

since there were no corroborating laboratory data as to histamine content of the blood or the changes resulting from the therapy. Laboratory facilities were not available to make these determinations.

A large group of pregnant women should be thoroughly studied throughout pregnancy, with histamine and histaminase determinations, to ascertain if changes can be detected before symptomatic signs appear and what changes occur with the use of antihistamines, before any final conclusions can be drawn.

References

1. Karnaky, K. J.: M. Rec. & Ann. **35**: 851, 1941.
2. Smith, O. W., Smith, G. van S., and Horwitz, D.: AM. J. OBST. & GYNEC. **51**: 415, 1946.
3. Rosenblum, G., and Melinkoff, E.: West. J. Surg. **55**: 597, 1947.
4. Bartholomew, R. A.: Mod. Med. **19**: 104, 1951.
5. Hofbauer, J.: AM. J. OBST. & GYNEC. **12**: 159, 1926.
6. Barsoum, G. S., and Gaddum, J. H.: J. Physiol. **85**: 1, 1935.
7. Marcou, I., and Atanasiu-Vergu, E.: Bull. Acad de méd de Roumanie **3**: 19, 1937.
8. Effekemann, G., and Werle, E.: Zentralbl. f. Gynäk. **64**: 1220, 1940.
9. Giudici, E.: Ann. di Obstet. e ginec. **59**: 611, 1937.
10. Marcou, I., Chiriceanu, D., Cosma, G., Gingold, N., and Parbon, C. C.: Paris méd. **46**: 371, 1938.
11. Ahlmark, A.: Lancet **2**: 406, 1944.
12. Danforth, D. N.: Am. J. Physiol. **119**: 295, 1937.
13. Kapeller-Adler, R.: Lancet **2**: 745, 1949.
14. Kapeller-Adler, R.: Biochem. J. **48**: 99, 1951.
15. McElin, T. W., and Horton, B. T.: Am. J. M. Sc. **218**: 432, 1949.
16. Javert, Carl T., and Finn, William F.: Texas State J. Med. **46**: 410, 1950.

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INFANTS DELIVERED BY CESAREAN SECTION*

A Re-evaluation After Ten Years of Some Problems Found in Infants Delivered by Cesarean Section

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IN 1942 a report[1] was made on the difficulty in beginning respirations seen in a series of 100 consecutive infants delivered by cesarean section. It has been ten years now since that report was published. Certain recommendations were made from that study with regard to the mother and infant.

The original report in 1942 stressed the fact that an analgesic given to the mother was given also to the infant. In addition it was suggested that the lack of compression of the fetus by labor contractions deprived that infant of a certain amount of conditioning to enable him readily to change from an intrauterine existence to an extrauterine life. At that time it was believed that this conditioning of the infant consisted in varying the diffusion gradients of oxygen and carbon dioxide which served to prime the respiratory center to take over on delivery of the infant. A trial of labor was suggested.

Recently other authors have recognized that the infant born by cesarean section may be handicapped and have recommended different methods of handling when delivery is by cesarean section. Gellis, White, and Pfeffer[2] recommend gastric suction, believing that the infant ingests large amounts of amniotic fluid, which is followed by regurgitation and aspiration. Later Gellis suggested that in addition mist be used to help the cesarean section infant. Landau, Goodrich, Francka, and Burns[3] believe that hematogenic shock is a contributing factor in the mortality of infants delivered by cesarean section. They recommend placental suspension and drainage for at least ten minutes whereby the infant is supplied up to an additional 90 c.c. of blood.

The present study was undertaken to determine if in the past ten years the recommendations with regard to handling this type of delivery and to treating the infants delivered by cesarean section have helped. As in the study of cesarean section infants made in 1942, this is a consecutive series of 100 infants delivered by cesarean section in the St. Joseph's Maternity Hospital in Houston, ending Dec. 31, 1952. In this hospital almost all of the deliveries are of private patients and are handled by obstetricians. Subsequent care of the infant is as a rule in the hands of a pediatrician. This study therefor represents a cross section of the method of handling private cesarean section patients and their newborn infants in this community for this period.

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Ft. Worth, Feb. 13, 1953.

More patients were delivered of the third and fourth infant in 1952 (Table I). The indications for cesarean section are essentially the same in 1952 as in 1942 (Table II).

TABLE I. PARITY OF PATIENTS

PREGNANCY	1942	1952
First	66	26
Second	26	34
Third	3	24
Fourth	1	12
Fifth	4	4

TABLE II. INDICATIONS FOR CESAREAN SECTION

INDICATION	1942	1952
Cephalopelvic dystocia	27	26
Contracted pelvis	23	4
Elderly primipara	12	2
Previous section	6	37
Pre-eclampsia	8	5
Nephritic toxemia	4	2
Placenta previa	4	8
Funnel pelvis	3	0
Placentae ablatio	3	2
Test of labor—no progress	3	1
Fetal distress	2	7
Cervical dystocia	2	4
Nephrosis	1	0
Dwarfism	1	0
Diabetes	0	1
Erythroblastosis fetalis	0	2
Premature separation of placenta	0	8
Polyhydramnios	0	1
Shock	0	3

Table III shows the numbers of patients who received analgesics. In 1942 fifty-one in the series of 100 patients received no analgesic. In 1952 only 20 patients received no analgesic. There has been a great increase in the use of Demerol, 76 of the 1952 series of 100 patients having received this analgesic. There has been a considerable decrease in the use of Nembutal and Pantopon.

TABLE III. ANALGESICS USED

TYPE	1942	1952
None	51	20
Nembutal or Seconal with Pantopon	19	4
Nembutal alone	17	0
Pantopon and morphia	8	0
Amytal	2	0
Luminal Sodium	1	0
Sodium bromide	1	0
Demerol	0	76

The anesthetics used are shown in Table IV. There has been a decrease in the use of cyclopropane from 69 to 39 patients, with nitrous oxide being used twice instead of 13 times as in 1942. There has been a decrease in the incidence of use of ether from 12 patients to 5. In 1942 only one patient in the series of 100 cesarean sections reported was delivered with spinal anesthesia, in 1952 sixty-one were delivered with this means.

TABLE IV. ANESTHETICS USED

TYPE	1942	1952
Cyclopropane	69	39
Nitrous oxide	13	2
Ether	12	5
Ethylene	9	0
Spinal	1	61

Table V shows the number of infants requiring initial resuscitation in the years 1942 and 1952. There has been a decrease from 42 in 1942 to 28 in 1952, which is believed to be directly due to the changes in types of analgesics and anesthetics.

TABLE V. NUMBER OF INFANTS WHO REQUIRED INITIAL RESUSCITATION

NUMBER OF SECTIONS	YEAR	TOTAL	MALE	FEMALE
100	1942	42	20	22
100	1952	28	15	13

In 1952, 37 infants showed delayed pulmonary symptoms of grunting, cyanosis, retraction of the chest, weak cry, and death of 2 with hyaline membranes. The incidence for this type of late difficulty is not available for 1942. Table VI shows this incidence.

TABLE VI. NUMBER OF INFANTS WHO SHOWED DELAYED DIFFICULTY

NUMBER OF SECTIONS	YEAR	NUMBER
100	1942	?
100	1952	34
(Symptoms: grunting, edema, cyanosis, chest retraction, convulsions, weak cry)		

Table VII shows the weights of infants in the 1942 series and the 1952 series. The numbers of infants in the different weight groups are essentially the same.

TABLE VII. WEIGHTS OF INFANTS

WEIGHTS (POUNDS)	1942	1952
Below 4	1	3
4 to 5	9	9
5 to 6	15	14
6 to 7	20	22
7 to 8	24	31
8 to 9	18	10
9 to 10	12	10
Above 10	1	1

Table VIII is a very interesting one. It was suggested in 1942 that, if possible, a trial of labor be given in an effort to minimize difficulties of the infant after delivery by cesarean section. In 1942 only 3 patients were subjected to a trial of labor. None of their infants had any difficulty. In 1952, 30 patients had trials of labor for varying periods. Of the 37 infants who had delayed pulmonary symptoms as shown in Table VI, 70 per cent had not been through a trial of labor, 19 per cent had been through a trial of labor of from one to eight hours, and 11 per cent through a trial of labor of from nine to

TABLE VIII. INFANTS WHO HAD LATE DIFFICULTY AFTER DELIVERY

DURATION OF LABOR	NUMBER	PERCENTAGE
None	26	67
One to eight hours	7	19
Nine to twenty hours	4	11
Total	37	100

(Symptoms of late difficulty: grunting, edema, cyanosis, chest retraction, convulsions, weak cry, death)

The 4 stillborn infants were not included in this group. The 2 infants who died with hyaline membranes in the alveolar sacs were not subjected to pressures in a trial of labor.

twenty hours. Table VIII shows that of the group of infants having delayed pulmonary symptoms only 11 per cent had trials of labor of from 9 to 20 hours.

It was noted that a considerable number of infants born by cesarean section were wet and would bring up mucus. Some mucus was thin and clear, some mucus was thick and purulent appearing. The incidence of infants in the series in 1952 was compared with a series of infants processed in the Air Lock. This is illustrated in Table IX. The incidence of cesarean section infants who brought up fluids is essentially the same as that which occurred in the premature infants processed in the Air Lock. This rate is two and one-half times the incidence of term infants who bring up fluids when processed in the Air Lock. These fluids are thought to be coming from the infant's pulmonary tree. It seems likely, therefore, that some mechanism lacking in delivery by cesarean section predisposes the term infant delivered by cesarean section to a condition of the pulmonary tree similar to that of the premature infant.

The Air Lock was used in the processing of 14 infants in the 1952 series. Stomach suction was used on 2 infants, a very small amount being obtained in one and about 5 c.c. in the other. Mist was used on no infant. Elevation of the placenta in an effort to fill as completely as possible the infant's circulatory system was not used. In how many instances the cord was stripped was not indicated on the histories. It could have been done a number of times and doubtless was done.

TABLE IX. FLUIDS EXPRESSED IN PROCESSING HANDICAPPED NEWBORN INFANTS

NUMBER OF INFANTS	METHOD	FLUIDS EXPRESSED
121 Term infants	Air Lock (4)	15 (12.4%)
125 Premature infants	Air Lock (4)	38 (30.4%)
100 Infants born by cesarean section	Self	30 (30 %)

In the group of 18 infants who went through a trial of labor of 8 hours or more, only one brought up mucus, as compared to 29 infants who brought up mucus in the remaining group of 82 infants subjected to no pressures by a trial of labor of 8 hours or more.

Four infants in this series from 1952 were stillborn. In 1942 there were no stillborn infants in the series reported. In 1952, 2 infants of this series of 100 died, one a premature infant of 3 pounds, 6 ounces, and one a term infant of 6 pounds, 6 ounces. Autopsies were performed on both infants and the essential findings were hyaline membrane disease of the newborn and resorption atelectasis.

Comment

Since 1942 there have been some changes in the infant seen after delivery by cesarean section.

In 1952 there are fewer infants who require initial resuscitation. There still remain a considerable number who show delayed difficulty.

The mothers are a little older and there is an increase in the number of cesarean sections performed on the individual patient.

In 1942 more patients were given no analgesic. For the most part the increase in the use of analgesics has been in the use of Demerol.

In 1942 only one patient was delivered with the use of a spinal anesthetic. In 1952, 61 patients were delivered under spinal anesthesia.

It seems advisable now to review briefly the physiological steps in the start of the functioning of the lungs to enable the infant to carry on an extrauterine life. Here is an organ that must take over on very short notice and function adequately but which does not reach full functional capacity at birth, but acquires this capacity over a period of time.

In the lung of the fetus at birth two things must take place. Pulmonary circulation and pressures must be established, and alveolar sacs in sufficient number must be expanded to allow an exchange of oxygen and carbon dioxide to enable the infant to survive. There is no reason not to believe that both changes aid each other in their functioning to permit extrauterine life.

A review of the cellular development of the fetal lung is desirable at this point. The eventual air spaces in the lung of the small fetus are structures which shortly before birth are tightly lined by low cuboidal cells.[6] The alveolar sacs of the infant born at term per vaginam are as a rule not lined with these low cuboidal cells. Thus, by a change in the shape of the cells lining the alveolar sacs in the infant delivered normally a more favorable condition is set up, allowing not only a closer approximation of the lower pulmonary capillaries to the air sacs, but, after the process of flattening, apparently a greater surface is made available by the cells lining the alveolar sacs for the exchange of oxygen and carbon dioxide. Such a metamorphosis may well prevent leakage by the pulmonary capillaries into the alveolar sacs, and at the same time provide a means of maintaining the pulmonary pressure.

Potter[6] states that in the young fetus the capillaries push between the low cuboidal cells and lie in contact with the air spaces. When this is done and there is little flattening of the alveolar cells lining the air sacs, the opportunity to maintain a pulmonary pressure is decreased, leakage is easier, and the ability of the alveolar sacs to function in the exchange of oxygen and carbon dioxide will be seriously impaired.

The premature infant delivered from below does not have an optimal number of low cuboidal cells mature enough for flattening, consequently there should be an increase in the number of these infants who bring up pulmonary fluids.[4] In cesarean section infants not subjected to pressures developed by a trial of labor for over 8 hours, the incidence of bringing up fluids after delivery

is essentially the same as that found in premature infants. This suggests that pressures generated in labor flatten some alveolar cells if the pressures are maintained over a sufficient length of time.

It is recognized that hyaline membranes are seen more frequently in premature infants and in term infants delivered by cesarean section. They are practically never found in infants prior to delivery or in infants who die during the first hour of extrauterine life. Gruenwald[7] has termed the hyaline membrane an "eosinophilic herring." When it is realized that the infant has to maintain a certain pulmonary pressure, and perhaps a high one at that, immediately after birth, the hyaline membrane by plugging any leaks of the pulmonary capillaries may initially be of considerable value to the infant. Only when such a membrane is so widespread that it interferes with a progressive flattening of the low cuboidal cells, or with an adequate exchange of oxygen and carbon dioxide is it a threat to the life of the infant. Many clinicians have seen premature infants and cesarean section infants who show all the classical signs of hyaline membrane difficulty recover, and apparently become entirely normal. Without doubt in those infants the hyaline membrane may have prevented considerable leakage of fluids from the pulmonary capillaries into the open alveolar sacs and directly aided in maintaining adequate pulmonary pressures.

Summary

1. A series of 100 consecutive newborn infants delivered by cesarean section ten years after a previous study of a like group of infants is reported from a private hospital.

2. There were 4 stillborn infants in this group, and 2 deaths. Both infants who died after delivery showed hyaline membranes on postmorten examinations.

3. Analgesics have changed and their use has increased.

4. The use of spinal anesthesia for delivery has increased from 1 case in 1942 to 61 in 1952.

5. Use of a trial of labor increased from 3 cases in 1942 to 30 in 1952.

6. Of the infants who had late difficulty after cesarean section, 70 per cent had no trial of labor, 19 per cent had a trial of labor of from one to 8 hours, and 11 per cent had a trial of labor of from 9 to 20 hours.

7. In this series of 100 consecutive infants born by cesarean section the duration or lack of pressures developed during labor had an important influence on whether, after delivery by this method, the infant would or would not develop late difficulty.

References

1. Bloxsom, Allan: J. Pediat. 20: 215, 1942.
2. Gellis, S. S., White, P., and Pfeffer, W.: New England J. Med. 240: 533, 1949.
3. Landau, Daniel B., Goodrich, Howard B., Francka, W. G., and Burns, Francis R.: J. Pediat. 36: 421, 1950.
4. Bloxsom, Allan: M. Rec. & Ann. 46: 184, 1952.
5. Cooley, Denton: Personal communication.
6. Potter, Edith L.: Pulmonary Hyaline Membranes, Report of the Fifth M and R Pediatric Research Conference, pp. 22-24, 1953.
7. Gruenwald, Peter: Reference 6, page 71.

ECTOPIC PREGNANCY*

An Analysis of 70 Cases

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ECTOPIC pregnancy still causes maternal death[6] despite the remarkable advances in anesthesiology, availability of blood banks, and excellent pre- and postoperative care. This justifies a statistical review of cases, since new information may be instrumental in reducing maternal mortality.

There were 70 cases of ectopic pregnancy at St. Joseph's Hospital during the years 1950-1952. The types and sites of the ectopic pregnancies are shown in Table I. The total number of deliveries for the same period of time was 18,446, an incidence of one ectopic pregnancy in 264 deliveries. Laparotomy was performed in 63 cases; one, an unruptured ectopic pregnancy in the distal end of the Fallopian tube, was removed with the aid of culdoscopy through the posterior cul-de-sac.

TABLE I. DISTRIBUTION OF CASES OF ECTOPIC PREGNANCY

Tubal pregnancy	56
Tubal abortions	7
Interstitial pregnancy	4
Ovarian pregnancy	2
Cervical pregnancy	1

Two patients, subjected to laparotomy, proved to have tubal abortions. Five other patients passed decidual casts, were kept under observation, and were classified as having probable tubal abortion. Three of these also had a curettage.

Signs and Symptoms

An evaluation of signs and symptoms based on 130 cases of ectopic pregnancy was reported by Bell and Ingersoll.[1] The cardinal signs and symptoms were considered to be pain, bleeding, adnexal mass, and amenorrhea, each appearing in a varying percentage of the total cases. Also, clinically, these patients were classified in two groups: those in shock, and those not in shock. These 70 cases were analyzed on a similar plan.[1, 4, 5]

Pain in the lower abdomen was so consistently present (68 of 70 cases) that it may well be considered a pathognomonic sign. Only two patients did not have pain, and these were among those classified as having "probable tubal abortions." The diagnosis of ectopic pregnancy should be guarded without the history, or presence, of pain. *Bleeding* was the next dependable sign, and

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Fort Worth, Feb. 13-14, 1953.

was present in 80 per cent of the cases. This varied from spotting to menorrhagia, with or without intra-abdominal hemorrhage. A *mass in the adnexa* or cul-de-sac was detected in 68 per cent. The least dependable or least present symptom was amenorrhea. Only 16 cases, or 23 per cent, had a clear-cut history of amenorrhea. The findings are summarized in Table II.

TABLE II. SIGNS, SYMPTOMS, AND FINDINGS

Signs and Symptoms (70 Cases).—		
Pain	68 cases	97%
Bleeding	56 cases	80%
Mass	48 cases	68%
Amenorrhea	16 cases	23%
Findings.—		
Ruptured	40	
Not ruptured*	16	
Shock	19	
No shock	51	
RBC less than 3.5 million per c.mm.	18	
RBC over 3.5 million per c.mm.	52	

*Tubal abortions, cervical pregnancy, etc., not included.

It is noteworthy that there was no direct correlation between the number of patients admitted in shock (19) and the number of ruptured tubal pregnancies found at operation (40). This is important for it is in the group with ruptured ectopic pregnancy without the clinical manifestation of shock that the grave danger of minimizing blood loss lies. Some of these were merely oozing blood and bleeding was not sufficient to cause shock. The site of rupture may heal, and bleeding may occur in varying amounts over a period of several weeks. Compensatory mechanisms of the body may avoid acute shock. Nevertheless, chronic blood loss with chronic tissue anoxia may result in irreversible changes in vital organs, and make the prognosis even less favorable. Beware of the patient with a suspected ectopic cyesis, who gives a history of symptoms for several weeks, but who clinically "looks good." It is not unknown to have chronic blood loss in a ruptured tubal pregnancy with a hemoperitoneum to 2,000 ml. without the clinical manifestation of shock.[6]

There was the expected correlation between the number of patients with shock (19) and the number of patients with a red blood cell count of less than 3.5 million per cubic millimeter (18). (The patient with the interstitial pregnancy illustrated was in shock and had a count of 3.7 million.) Adequate blood replacement for this group with ruptured ectopic pregnancy with shock, therefore, implies an average minimum of 1,000 ml.

Other Pathological Findings

Salpingitis.—Chronic inflammatory disease has long been attributed as a chief cause of ectopic pregnancy and was the most common attending finding in this series of cases. According to Novak,[2] the etiological factor is primarily a mechanical one, narrowing the lumen and producing blind alleys in the tube. Also to be considered is a reduction of ciliary movement with resulting retardation of the progress of the ovum.

Ovarian Cyst.—Some form of ovarian cyst was present in 20 cases, or 28 per cent. The presence of an ovarian mass, therefore, should not make one abandon the diagnosis of ectopic pregnancy. Eight of these cysts resected proved to be corpus luteum cysts of pregnancy. The corpus luteum is almost always sacrificed, and has been resected in early pregnancy[15] and in combined extrauterine and intrauterine pregnancy.[5] Care should be taken, therefore, (1) to rule out a normal intrauterine pregnancy and avoid resecting the corpus luteum, if possible; (2) to substitute endocrine replacement therapy if the corpus luteum is resected.

Chronic Periappendicitis.—Appendectomy at laparotomy for ectopic pregnancy is still a controversial point. However, in those cases where appendectomy was performed, microscopic evidence of chronic periappendicitis was found in 9 cases. This may be associated with the high incidence of chronic pelvic inflammatory disease, or be a direct result of peritoneal irritation from hemoperitoneum.

Bilateral Hematosalpinx.—This condition was found in 3 cases and illustrates the value of inspecting both adnexa at operation. Bilateral tubal pregnancy has been reported,[10] and this possibility must also be ruled out.

There were two cases of endometriosis, and two cases of fibromyomas of the uterus.

TABLE III. OTHER PATHOLOGICAL FINDINGS

Salpingitis		23 cases	33%
Ovarian cyst*		20 cases	28%
Corpus luteum	12		
Follicle cyst	11		
Hemorrhage cyst	2		
Dermoid	2		
Chronic periappendicitis		9 cases	13%
Bilateral hematosalpinx		5 cases	7%
Endometriosis		2 cases	
Fibromyomas of the uterus		2 cases	

*Multiple cysts present in same ovary in some cases.

Other Diagnostic Procedures

Dilatation and Curettage.—While curettage and examination under anesthesia are advocated by some authors,[1, 4] often the diagnostic difficulty of ruling out the presence of an intrauterine pregnancy makes one hesitate to use this procedure in these cases. Dilatation and curettage may be considered of value in the detection of a decidual reaction,[1] and was performed in 10 cases of this series.

TABLE IV. OTHER DIAGNOSTIC PROCEDURES

Dilatation and curettage	10
Colpotomy	2
Culdoscopy	2
Pregnancy test	2
Biopsy and frozen section	1

Culdoscopy and Colpotomy.—These procedures were done in two cases, and, in one, it was possible to remove the ectopic pregnancy vaginally. Thus

the patient was spared a laparotomy. Culdoscopy is a valued adjunct to our available diagnostic avenues in the management of ectopic pregnancy.[7, 9] Te Linde has stated that culdoscopy is not more frequently used for two reasons: laziness and fear of perforating a viscus. A third reason may be added, and that is simply that not a sufficient number of men are trained in the use of this procedure. All this, however, should not limit the proper place of culdoscopy in the management of ectopic pregnancy.

Pregnancy Tests.—The Aschheim-Zondek test or frog test was used in two cases. False positive tests, as, for example, with intrauterine pregnancy and ovarian cyst, or false negative tests are misleading, and have detracted from the real value of relying on pregnancy tests for aid in diagnosis.

Biopsy and Frozen Section.—This was done in a lesion which simulated early malignancy of the cervix, and proved to be a cervical pregnancy at seven weeks' gestation.

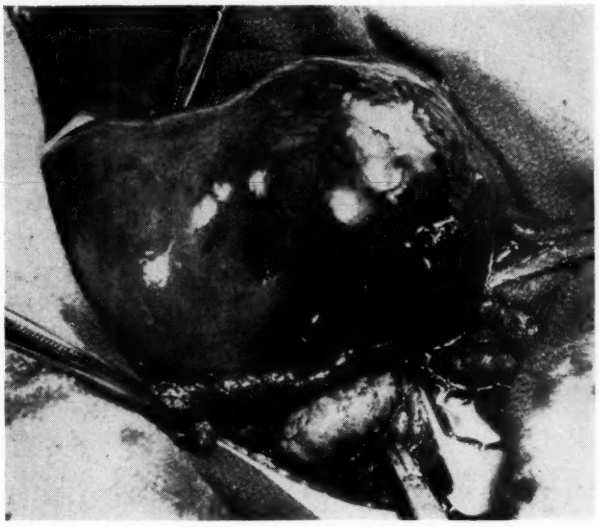

Fig. 1.—Interstitial pregnancy, showing incomplete rupture at junction of left tube with the corpus uteri.

Interstitial Pregnancy

Because of its protected location, interstitial pregnancy usually develops for a longer period of gestation before it ruptures or extends into the uterine cavity. Rarely is it diagnosed and terminated prior to rupture. Four cases of interstitial pregnancy were found in this group of cases. All 4 were found ruptured at operation. All 4 patients were in shock. The red blood cell count was below 3.5 million, in 3 cases. One, which progressed to 12 weeks' gestation before incomplete rupture occurred, is illustrated.

Case N. 5617.—Mrs. N. M., a 26-year-old white woman, was admitted to the hospital on Oct. 9, 1952, with a history of onset of abdominal pain at 9 that morning, followed by weakness and fainting. The blood pressure was 80/50, pulse 120, and weak. A definite mass, difficult to outline, was palpable in the left adnexa. Her last menstrual period was July 19, 1952. (The period of gestation was confirmed by an 8 cm. fetus found at laparotomy.)

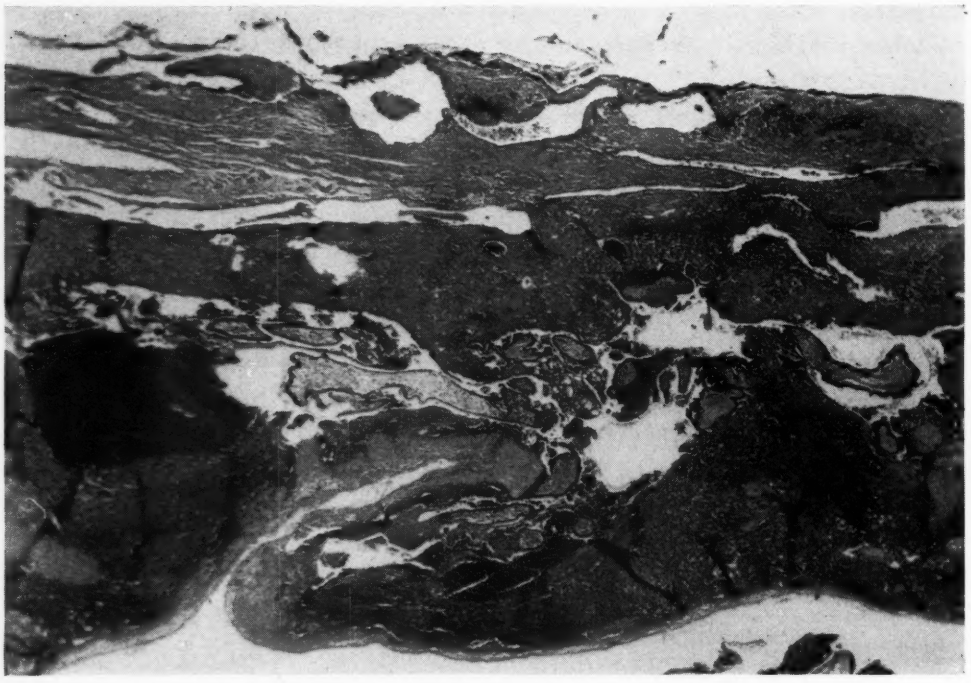

Fig. 2.—Invasion of myometrium by chorionic villi. (×18.5. Reduced one-fourth.)

Mortality Rate From Ectopic Pregnancy

There was one maternal death in this group of 70 cases of ectopic pregnancy (1.4 per cent). Recent reports from the different parts of the country average from 1.2 per cent[10] to 1.5 per cent.[11]

Treatment

The main difference of opinion in the treatment of ectopic pregnancy is conservative management (Barker and Brown[13]) versus immediate surgery (Keettel[14]). While it is not the purpose of this paper to discuss treatment in detail, a few comments will be made. Aside from the controversy as to when to undertake surgery, the generally accepted treatment revolves about the following:

1. Transfusions.—Immediate replacement with compatible blood should be undertaken to combat shock, pre- and postoperatively. Whole blood under pressure should be given if necessary. Adequate and complete blood replacement is also important for a smooth convalescence.

2. Oxygen.—Oxygen should be given pre- and postoperatively to combat acute or chronic tissue anoxia.

3. Antibiotics and Chemotherapy.—Their use may be prophylactic, as indicated by the high incidence of concomitant pelvic inflammatory disease, or they may be used in the presence of obvious sepsis.

4. Surgery.—It cannot be emphasized too strongly that the site of ectopic pregnancy should be removed and required surgery only should be done. In general, it is unwise to perform appendectomy, suspension, or other unnecessary surgical procedure in the face of an ectopic pregnancy, ruptured or not. The importance of inspecting both adnexa has already been mentioned, and occasionally a tubal plastic procedure may be justified. In the presence of massive hemorrhage, prompt hemostasis is imperative, and usually the involved tube and ovary are removed. The ovary may be saved if its blood supply is preserved.

At present it is considered best to remove blood and clots from the peritoneal cavity. It has been shown that rapid hemolysis occurs in blood present in the peritoneal cavity, and that it is not necessarily a source of hemoglobin and red blood cells.[14] Bacterial contamination is high, and autotransfusion is, therefore, not to be desired.

Ultrarapid Blood Transfusion and Ectopic Pregnancy

Since the calamity of maternal loss from ectopic pregnancy invariably results from shock from blood loss, acute or chronic, or any of the complications thereof, it appears logical to evaluate and use any means which gives promise of improved treatment of this condition. Pierce and associates[8] published and evaluated a method of *intravenous* ultrarapid blood transfusion, which obviates the difficulties of intra-arterial transfusion, and offers the same advantages. The method is one of utilizing oxygen under pressure, which is placed within the tranfusion bottle through the air vent, thus forcing the blood rapidly into the vein. The main advantage gained is the rapid increase in the circulatory volume. Ruptured ectopic pregnancy, with sudden circulatory collapse from severe hemorrhage, presents an ideal indication for such a method of transfusion. General tissue anoxia, which is directly proportional to the length of time the patient is in shock, and which, if prolonged, causes irreversible changes in vital organs, would be reduced. In cases of chronic blood loss, without the clinical manifestation of shock, this method of transfusion may be of value as a prophylactic measure.

Conclusions

1. Seventy cases of ectopic pregnancy are reported with clinical and statistical analysis.

2. The most common signs and symptoms were abdominal pain (97 per cent), vaginal bleeding (80 per cent), adnexal mass (68 per cent), and amenorrhea (23 per cent).

3. There is grave danger of minimizing blood loss in ruptured ectopic pregnancy without the clinical manifestation of shock. Chronic blood loss should be treated with the same diligence and care as acute shock.

4. There was a direct correlation between acute shock and a red blood cell count of less than 3.5 million per cubic millimeter. Adequate blood replacement is estimated at an average minimum of 1,000 ml. for this group of cases.

5. Other concomitant pathological findings were salpingitis (33 per cent), ovarian cyst (28 per cent), chronic periappendicitis (13 per cent), bilateral hematosalpinx (7 per cent). Endometriosis was found in 2 cases, and fibromyomas of the uterus in 2 cases.

6. Ruptured ectopic pregnancy, with acute or chronic shock, presents a real indication for the use of intravenous ultrarapid blood transfusion.

7. There was one maternal death in this group of 70 cases (1.4 per cent).

The case report and illustrations were made possible through the kindness of Dr. Joseph P. Salerno. I also wish to thank Dr. Robert Johnston for his generous cooperation in the presentation of this paper.

References

1. Bell, J. W., and Ingersoll, F. M.: Am. J. Obst. & Gynec. 60: 174, 1950.
2. Novak, Emil: Gynecological and Obstetrical Pathology, Philadelphia, 1947, W. B. Saunders Company, p. 437.
3. Henderson, D. N., and Bean, J. L.: Am. J. Obst. & Gynec. 59: 1227, 1950.
4. Collins, Conrad G., Beacham, W. D., and Beacham, Dan W.: Am. J. Obst. & Gynec. 57: 1144, 1949.
5. Michaels, J. P.: Am. J. Obst. & Gynec. 57: 717, 1949.
6. Maternal Death, Ectopic Pregnancy, and Irreversible Shock, Bull. Margaret Hague Maternity Hosp. 4: 77, 1951.
7. Decker, Albert: Am. J. Obst. & Gynec. 63: 654, 1952.
8. Pierce, V. K., Robbins, G. F., and Brunschwig, A.: Surg., Gynec. & Obst. 89: 442, 1949.
9. Te Linde, R. W., and Rutledge, F.: Am. J. Obst. & Gynec. 55: 102, 1948.
10. Hofmeister, F. J., and Hultman, C. A.: Wisconsin M. J. 51: 166, 1952.
11. Word, B.: Surg., Gynec. & Obst. 92: 333, 1951.
12. Pisani, B. J.: Surg., Gynec. & Obst. 95: 149, 1952.
13. Barker, J., and Brown, W. E.: Current Therapy, p. 715, 1952.
14. Keettel, W. C.: Current Therapy, p. 716, 1952.
15. Glasser, John H. W.: Bull. Margaret Hague Maternity Hosp. 5: 112, 1952.

FACE PRESENTATION*

A Review of 94 Cases

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THE infrequency of face presentation in the practice of the average physician renders it difficult for him to formulate a definite plan of management on the basis of personal experience. Many excellent reviews on face presentation and its management have appeared in the literature in the past few years. Since most of the articles on this abnormal presentation, with its attendant difficult problems, consist of critical analyses of statistics of charity institutions associated with university medical centers, it was felt that definite benefit could be obtained from a consideration of the management of this uncommon obstetrical problem occurring in a private maternity center. The purpose of this paper is to formulate a method of management based upon a review of cases of face presentation that occurred during a ten-year period at St. Joseph's Maternity Hospital, Houston, Texas.

Incidence

There were 94 cases of face presentation during the period ending with December, 1950. These occurred in the delivery of 58,555 white in-patients, a ratio of 1:623 deliveries, or an incidence of 0.160 per cent. This figure is slightly less than that recorded by other authors, and is significantly less than the 0.2 to 1 per cent quoted by standard textbooks.[1] We felt this lower incidence to be due to hospital admissions that were limited to members of the Caucasian race. Large series by others include Negro patients, in whom there is a greater incidence of pelvic contracture. A comparison of our incidence with that of others is shown in Table I.

TABLE I. INCIDENCE OF FACE PRESENTATION AS CITED IN THE LITERATURE

	DELIVERIES	FACE	RATIO	PERCENTAGE
Posner and Buch, Harlem Hospital Series, 1943[4]	48,000	87	1:529	0.190
Rudolph, Philadelphia Lying-In, 1947[6]	35,163	61	1:576	0.174
Reddoch, Charity Hospital, New Orleans, 1948[5]	88,114	160	1:550	0.184
King and Segar, Medical School, Univ. of Maryland, 1948[3]	28,169	51	1:552	0.181
Hellman, Epperson, and Connally, Johns Hopkins, 1950[2]	65,930	141	1:468	0.213
Tucker, Salomkin, and Abrams, Chicago Maternity Center, 1950[8]	39,687	73	1:556	0.184
Present series, St. Joseph's Maternity, Houston, Texas, 1951	58,555	94	1:623	0.160

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Austin, Feb. 14-16, 1952.

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Etiology

These cases were carefully examined for factors which might be causative of face presentation. These factors along with occurrence of face presentation in age groups are shown in Table II.

TABLE II. AGE INCIDENCE OF FACE PRESENTATION

AGE	PRIMIPARAS	MULTIPARAS	TOTAL
20 and under	10	4	14
21-30	19	34	53
31 and over	5	22	27
Total	34	60	94

The age and parity groupings of the occurrence of face presentation are shown as a matter of interest. There were twice as many multiparas in all age groups considered, indicating that multiparity with its accompanying loss of abdominal and uterine muscle tone, and not age, is a factor. From the chart on etiology (Table III) it will be noted there are 70 instances where a factor was found which was thought to be causative of face presentation. A number of these factors occurred in combination with one another, such as parity, polyhydramnios, and monsters. It will be noted that there are a number of cases in which there is no explanation for the occurrence of the presentation. There were several instances of contraction ring, and cord around the neck of the infant. These were considered to be a result of the presentation, or a coincidental finding, since the occurrence was no greater than on the service as a whole. The major factors in the production of face presentation in this series, in their order of frequency, were multiparity, polyhydramnios, monsters, face secondary to brow, extremely large babies, extremely small babies, and pelvic architecture. One instance of a second twin was recorded.

TABLE III. ETIOLOGICAL FACTORS IN FACE PRESENTATION

	PRIMIPARAS	MULTIPARAS	TOTAL
Parity (gravida iv and more)	0	14	14
Polyhydramnios	6	5	11
Monsters	5	5	10
Face secondary to brow	3	7	10
Small babies (5½ pounds and under)	3	6	9
Large babies (9 pounds and over)	2	7	9
Pelvic architecture:			
Android	0	2	2
Anthropoid	0	2	2
Platypelloid	1	0	1
Justominor	1	0	1
Second twin	0	1	1

Position

When the diagnosis of face presentation was made (usually late in the first stage of labor), engagement was found to be in the mentoanterior position 49 times (52 per cent), in the mentotransverse 7 times (7½ per cent), and in the mentoposterior position 18 times (20 per cent). The occurrence in parity groups is shown below in Table IV.

TABLE IV. POSITION OF THE FACE IN RELATION TO PARITY

	PRIMIPARAS	MULTIPARAS	TOTAL
Left mentoanterior	8	13	21
Left mentotransverse	2	0	2
Left mentoposterior	5	5	10
Right mentoanterior	7	16	23
Right mentotransverse	1	4	5
Right mentoposterior	1	3	4
Mentoanterior unclassified	1	4	5
Mentoposterior unclassified	2	2	4
Not recorded	7	13	20
Total	34	60	94

Membranes

Premature rupture of the membranes occurred in 7 instances. The length of time prior to the onset of labor varied from 1 to 5 days. It is possible that premature rupture of the membranes may be responsible for the production of this presentation in a few instances. In 47 cases the membranes ruptured spontaneously during labor. Artificial rupture of the membranes was practiced in 26 instances to improve the quality of labor. In 10 instances the membranes were ruptured in the delivery room.

Labor

The first stage of labor was 24 hours and less in 78 cases (83 per cent), 24 hours and more in 12 cases, and was not stated in 2 cases. The longest labor in this series lasted 38 hours in a gravida ix. The shortest labor was of 1 hour and 45 minutes' duration in a gravida iii. There were 13 instances in which the labor lasted 4 hours or less. The average length of the second stage of labor was 23 minutes. In only 8 instances was the second stage of labor markedly prolonged (1 to 2 hours). In one instance there was a test of labor of 12 hours' duration. Labor in parity groups is shown in Table V.

TABLE V. DURATION OF LABOR IN FACE PRESENTATION

	PRIMIPARAS	MULTIPARAS	TOTAL
24 hours or less	24	54	78
24 hours or more	8	4	12
Not stated	0	2	2
Total	32	60	92

Delivery

In this discussion, it is advisable to point out that a large percentage of these cases were handled by general practitioners and that consultation is mandatory for this group in any case that is not making satisfactory progress, or if an abnormal presentation exists. In some instances, particularly in those cases where version and extraction were performed, consultants were not called until an emergency existed.

Seventy-one patients in this series were delivered from below without difficulty. Of these, 37 deliveries occurred spontaneously, 27 with aid of outlet forceps, and 7 by easy midforceps. High forceps were not employed in any

cases in this series. Manual flexion and conversion maneuvers to an occiput anterior position were performed in 2 instances, once in each parity group. Twelve versions and extractions were performed because of unsatisfactory progress after complete dilatation of the cervix had been reached. In three instances after a midforceps attempt, podalic version was performed as an emergency procedure because the cord had prolapsed. In the remaining instances, version and extraction were performed because of failure of the presenting part to become engaged. In contrast to findings in other series, the mentoposterior position was not a significant factor in failure of the presenting part to become engaged, except in those cases where cesarean sections or version and extraction were done. In this group, 50 per cent had mentoposterior positions. Eleven patients were delivered by cesarean section. Of these, 2 primiparas were sectioned without labor because of justominor pelvis and primary mentoposterior at the inlet. The remaining sections were performed because of fetopelvic disproportion and unsatisfactory progress during labor. Five sections were performed after a spontaneous labor of less than 24 hours and 4 were performed after a labor of 24 hours or more. The longest trial of labor before cesarean section was done was 30 hours.

TABLE VI. METHODS OF DELIVERY IN FACE PRESENTATION

	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	5	20	25
Spontaneous with episiotomy	2	10	12
Low forceps with episiotomy	9	15	24
Low forceps rotation with episiotomy	3	0	3
Midforceps	2	5	7
High forceps	0	0	0
Version and extraction	6	6	12
Cesarean section	7	4	11
Total	34	60	94

Nitrous oxide induction with cyclopropane was the anesthetic agent in a majority of these cases. Gas, oxygen, and deep ether anesthesia was used for podalic versions. There were no saddle blocks in this series, and only one spinal was used for a section.

Table VII shows the relationship of fetal and maternal morbidity and mortality to the methods of delivery.

Inspection of Table VII shows that there were no maternal deaths. The complications that followed other methods of delivery were negligible in comparison to the fetal and maternal complications following podalic version. There was a 50 per cent maternal morbidity and a 43 per cent fetal mortality following this operative procedure. Of the 21 infants that failed to survive, 2 were premature nonviable infants of less than 28 weeks' gestation, 2 were macerated stillborn infants, 12 had anomalies incompatible with life, and 5 were viable term-sized infants in good condition prior to attempts at delivery. This is a fetal mortality of 22 per cent. Correcting for anomalies and prematurity gave a corrected fetal mortality of 6.4 per cent for this presentation. This entire group of infants died from attempts at delivery by podalic version.

Morbidity following cearean section was proportional to the length of labor before operation was performed. It was interesting to note that delivery was spontaneous in all cases of anencephaly, and regrettable to note that cesarean section was performed in 2 cases of hydrocephalus. This might have been avoided if x-rays had been taken.

TABLE VII. RELATION OF FETAL AND MATERNAL MORTALITY AND MORBIDITY TO METHOD OF DELIVERY

	SPONTANEOUS	LOW FORCEPS	MID-FORCEPS	VERSION	SECTIONS
Maternal mortality	0	0	0	0	0
Maternal complications:					
Perineal lacerations	5	2	2	0	0
Puerperal morbidity:					
1 day fever	1	0	0	3	4
2-4 day fever	1	1	2	3	0
5-8 day fever	1	1	0	1	2
47 day fever	0	0	0	1	0
Cervical laceration	1	1	1	0	0
Hemorrhage with shock	0	0	0	4	0
Endometritis	0	1	0	5	0
Postpartum eclampsia with convulsions	1	0	0	0	0
Ruptured uterus	0	0	0	1	0
Pulmonary atelectasis	0	0	0	1	0
Fetal mortality:					
Anencephalic monster	10	0	0	0	0
Hydrocephalic	0	0	0	0	2
Premature (less than 28 weeks)	1	1	0	0	0
Macerated stillborn	2	0	0	0	0
Term intrapartum	0	0	0	4	0
Term neonatal	0	0	0	1	0
Fetal complications:					
Intracranial hemorrhage	1	0	1	1	0
Fractures	0	0	0	1	0
Cephalhematoma	0	0	1	0	0
Deep asphyxia	0	0	1	0	0

Weight of Infants

There were 9 infants who weighed less than 2,500 grams and also 9 infants weighed more than 4,000 grams. Fifty-nine infants were in the normal range, weighing from 2,500 to 4,000 grams. The largest baby delivered weighed over 4,600 grams, the smallest baby weighed 1,000 grams. Seventeen were not weighed.

Management

From the foregoing review one may conclude that an early diagnosis of face presentation is most important in its management. The use of the fourth maneuver of abdominal palpation is a distinct aid in the correct diagnosis of this presentation. This abnormal presentation should be considered whenever one finds the presenting part high, the groove felt between the vertex and back, and the unusually long ovoid of the uterus. The characteristic findings of the nose, eyes, and mouth on rectal or vaginal palpation are confirmatory of such a diagnosis. If doubt exists as to the presentation after a careful, sterile vaginal

examination, x-ray examinations should be employed to confirm presentation and position and to rule out fetal anomalies, and also to give an adequate radiological estimation of pelvic capacity. As soon as the diagnosis of this presentation has been made, prophylactic antibiotic and chemotherapeutic measures should be employed, as well as control of fluid and electrolyte balance. These patients are all potential candidates for cesarean section and should have close clinical supervision during labor. Since a great majority of these patients deliver from below without difficulty, a trial of labor in an adequate pelvis is indicated. All cases of fetopelvic disproportion should be evaluated by means of x-ray pelvimetry. Cases of elderly primiparas and absolute fetopelvic disproportion should be electively sectioned. In selected cases of relative fetopelvic disproportion, a trial of labor may be allowed as long as there is satisfactory progress without evidence of fetal or maternal distress. Cesarean section is the method of choice in these cases in which satisfactory progress does not occur. Podalic version, as well as difficult midforceps, does not seem indicated as a means of delivery because of the attendant dangers to both mother and infant.

Summary and Conclusions

1. The incidence of face presentation in this series was 0.160 per cent. This is a ratio of 1:623 deliveries.

2. Face presentation occurred twice as often in multiparas as in primiparas.

3. The mentoanterior position was approximately three times as frequent as the mentoposterior.

4. There was a 13 per cent incidence of fetal anomalies in this series.

5. Multiparity, polyhydramnios, monsters, face presentation secondary to brow presentation, extremely large babies, extremely small babies, pelvic architecture, and possibly premature rupture of the membranes played a part in etiology of this presentation.

6. In 70 per cent of these cases, vaginal delivery occurred without difficulty.

7. Version and extraction do not seem indicated as a means of delivery because of the associated high fetal mortality and maternal morbidity.

8. Cesarean section should be considered as a method of choice in face presentation, where satisfactory progress does not occur.

References

1. Eastman, Nicholson J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., pp. 801-810.
2. Hellman, L. M., Epperson, John W., and Connally, Frank: Am. J. Obst. & Gynec. 59: 831, 1950.
3. King, J., and Segar, B. E.: Bull. Univ. Maryland Med. School 33: 87, 1948.
4. Posner, A. Charles, and Buch, Irwin M.: Surg., Gynec. & Obst. 77: 618, 1943.
5. Reddoch, Joseph W.: Am. J. Obst. & Gynec. 56: 86, 1948.
6. Rudolph, Stephen J.: Am. J. Obst. & Gynec. 34: 987, 1947.
7. Titus, Paul: Management of Obstetrical Difficulties, ed. 4, St. Louis, 1950, The C. V. Mosby Company, pp. 587-591.
8. Tucker, Beatrice E., Salomkin, Mark, and Abrams, Bernard: Surg., Gynec. & Obst. 90: 109, 1950.

VAGINAL DELIVERY FOLLOWING CESAREAN SECTION*

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THE old dictum, "Once a cesarean section, always a section," is still adhered to by too many obstetricians. In reviewing the literature one cannot help but be impressed by this fact. Recent reports of surveys of the incidence of cesarean section in both large and small hospitals state that the indication, previous cesarean section, continues to be prominent on the list, in from 22.7 to 41.0 per cent of all sections done.

Since these statistics are for the period 1941-1950, they represent the current thought and practice of a large group of obstetricians. It is apparent that the high incidence of this indication for surgery is due to training and custom rather than to previous unfortunate experience, since the majority of the reports reveal that the incidence of uterine rupture during labor following previous classical cesarean section, the worst type of case to select for a trial of labor, is only 3 to 4 per cent. Proper selection of patients will, of course, reduce this percentage to a much smaller figure.

During the past decade, and more particularly during the three years just concluded, there has been a gradually increasing liberalization of the indications for cesarean section. This paper does not concern itself with the justification of the changing attitude and these remarks serve merely to indicate a trend. It necessarily follows that the increased number of operations performed will add materially to the growing number of patients who present the problem of pregnancy and delivery subsequent to previous cesarean section.

The development of obstetrics as a specialized field of medical practice has done much to reduce both the mortality and morbidity associated with childbearing. This is a fact of which we can all be justifiably proud; that we can do better is freely admitted by everyone. The development of conservative methods of handling some of our problems, such as placenta previa, toxemia, prolonged labor, and infected abortions, has had much to do with the record of annual improvement in technique.

There is a growing conservative element in our branch of medicine which is demonstrating that vaginal delivery subsequent to previous cesarean section is in many cases a rational procedure, and should be carefully considered prior to surgery. This group includes Schmitz, Cosgrove, Avilés, and others.

There is naturally opposition to any method deviating from standard procedure long established. The proponents of routine repeat section will most probably point out that the incidence of uterine rupture and its attendant

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Fort Worth, Feb. 13-14, 1953.

mortality will always be too high regardless of how it is reduced by proper patient selection. To evaluate this claim truly one must consider the ultimate outcome of actual rupture of the uterus. There is a distinct difference between rupture of a normal uterus and rupture through a poorly healed section scar. In the former, there is a sudden rupture through all coats of the uterus, extrusion of the fetus into the abdomen, partial contracture of the uterine muscle with disturbance of the placental site, profuse bleeding, and rapidly advancing hemorrhagic shock. The fetus is almost invariably killed and the maternal mortality is extremely high. In the case of rupture through a weak scar, the contents of the uterus are usually not extruded, the hemorrhage is minimal for a considerable period, and both the fetus and mother have an excellent chance if diagnosis and treatment are prompt and efficient. This is particularly true if the scar is located in the lower uterine segment.

The mortality following rupture through a cesarean scar is reported from zero to as high as 11 per cent by such investigators as Schmitz, Duckering, McLane, and Burkons. Repeating the incidence of rupture as approximately 3 per cent, one finds the mortality of pelvic delivery following section to be roughly 0.3 per cent. Comparison of this figure with the generally accepted one of the basic mortality in resection cases of 1 to 2 per cent reveals that under the worst conditions the pelvic delivery is a more conservative measure than repeat sections. This view is admittedly a highly controversial one and must necessarily be qualified by the condition that the patient must be under careful observation at all times by an experienced, competent obstetrician in a hospital equipped to meet all emergencies with the least possible delay. This latter point cannot be overemphasized.

The selection of patients for a trial of labor is secondary only to a wholly favorable hospital and professional environment. Each case must be evaluated separately and apart from all others and no attempt should be made to establish hard and fast rules concerning these patients.

Patients in whom the indication for previous cesarean section was absolute (contracted pelvis, or distorted pelvis due to injury) are not considered in this paper. They must of necessity be resectioned since this is the only possible solution to their problem.

There is a large group of women, however, in whom the operation was performed due to temporary modifiable causes; and a still larger group in whom the indication for surgery was erroneous or at best poorly advised. It is in these two groups that we consider our candidates for pelvic delivery.

In the selection of patients, the first consideration is the type of previous section. It is my policy, temporarily at least, to reject all patients who have had previous classical operations. This view is not shared by a considerable number of obstetricians interested in the subject. I also reject patients who give the history of several previous cesarean operations, believing that repeated assaults upon the uterine musculature are not conducive to the formation of strong scar tissue.

The type of postoperative convalescence is next considered. The actual hospital records are examined whenever feasible, rather than relying solely on the patient's history. A history of a febrile course, postpartum hemorrhage, or prolonged convalescence from any cause casts a doubt upon the advisability of pelvic delivery.

The type of patient from a general physical standpoint is an important factor. Those of hyposthenic habitus, with malnutrition or muscular weakness due to constitutional disease, usually form scars of substandard strength regardless of the site of incision.

The technical ability of the surgeon who performed the previous section should be considered as an important factor. It has been well demonstrated both clinically and experimentally that the strength of a well-healed scar is as great as the uterine muscle itself. An evaluation of the scar must necessarily depend somewhat upon the man who made the incision and repaired it.

Factors which should encourage trial of labor, and which also give the promise, at least, of a reasonably short labor, are: (1) early engagement of the presenting part, (2) beginning of effacement of the cervix, and (3) an anterior cephalic position. This is particularly true of women who have never delivered vaginally. Women who have delivered several children before having a section are usually considered prime candidates for trial; and, likewise, women who give the history of pelvic delivery subsequent to cesarean operations are usually easy to deliver from below. In regard to this latter group of patients, a word of caution is indeed proper. Eastman has called attention to numerous instances in which a baby has been delivered successfully through the vagina following previous section, and both the patient and her attending physician are lulled into a false sense of security in subsequent pregnancies, only to be rudely awakened by uterine rupture even prior to labor. The facts are that with each additional pregnancy and vaginal delivery the probability of spontaneous rupture of an old casarean scar increases. Therefore, the obstetrician should never relax his attention to minute details in the care of these women, regardless of the apparent ease of the previous delivery. Although in most instances economic conditions have decreased the size of the average American family, there is certainly a limit to the abuse an old scar should be expected to take. It would seem opportune to suggest sterilization after a reasonable number of successful vaginal deliveries.

In considering patients with the diagnosis of death or monstrosity in utero, one is faced with the greatest inconsistency in modern medicine. Many good obstetricians who will violently oppose pelvic delivery following section will attempt to deliver a dead fetus vaginally. This again is a product of custom and training rather than rational thinking. The delivery of a dead fetus, distorted in attitude, is frequently technically most difficult, as everyone present knows from experience. The salient fact of the whole matter is that the maternal danger of uterine rupture is identical regardless of the condition of the fetus in utero.

The patient selected for trial labor should usually be allowed to enter labor spontaneously. If conditions justify it, conservative induction of labor is not contraindicated. Rupture of the membranes should be avoided until early pelvic delivery is assured, since each patient is still a candidate for surgery until the fetus is delivered. Modification of the bacterial flora of the vagina by the use of antibiotics in the form of vaginal suppositories is a worthwhile practice, particularly in patients in whom the ultimate outcome is still questionable. In general, these patients are considered as any other patient in labor, and conditions of hyperdynamics or hypodynamics are modified by the use of antispasmodics or oxytocics as indicated. Attempt is made to control the labor to one of average contractions, progressing without unnecessary delay, and concluding in a period of twelve hours or less. At the end of this period, if the patient is not delivered, the case should be re-evaluated. Further trial of labor is not contraindicated if reasonable progress has been made. However, this is a good point at which to reconsider surgical intervention prior to maternal exhaustion and the necessity for the use of considerable amounts of supportive therapy.

Up to this point no mention has been made of the advisability of taking the patient and family into complete confidence prior to the trial of labor in order to avoid a possible emotional crisis in the event of failure of one method to terminate the pregnancy. All patients should be prepared both mentally and physically for surgery from the very beginning.

In a review of hospital statistics for the past twenty years, Cosgrove reports 117,000 deliveries, and 4,500 cesarean sections. Twelve ruptures occurred through previous scars, 6 prior to labor, and no deaths due to this complication. Six deaths occurred in the repeat section cases. Following 500 sections, 17 women (35.8 per cent) delivered 221 babies vaginally.

Avilés, whose statistics cover a ten-year period, reports 42,214 deliveries, 1,016 of which were sections, 20 ruptures through previous scars, 2 prior to labor, and 2 deaths, both attributed to hemorrhage and shock. Three hundred and sixteen patients delivered 429 babies following previous section, an incidence of 74 per cent.

For the past twenty years, Schmitz reports 36,293 deliveries, and 585 cesarean operations. There was a total of 10 ruptured uteri, 6 with section history, and 4 without section history. Thirty-two and six tenths per cent of 190 patients with a history of previous section were delivered vaginally. There was no mortality in the 6 cases of uterine rupture.

McLane found no uterine rupture and no maternal mortality in his series of 43 cases.

Duckering reported 8 cases of uterine rupture in previously sectioned patients with no maternal mortality.

It is almost universally true that the cesarean section-vaginal delivery ratio of small general hospitals in rural communities compares unfavorably with the statistics of the academically controlled teaching institutions. My own hospital belongs to the former group. A review of the statistics for the period 1946-1951 results in the following figures:

TOTAL DELIVERIES	SECTIONS	PERCENTAGE
6,210	389	6.2

A review of my own statistcs for the same period:

YEAR	TOTAL DELIVERIES	SECTIONS	PERCENTAGE	VAGINAL DELIVERY FOLLOWING SECTION
1946	326	13	3.9	1
1947	325	18	5.5	0
1948	369	13	3.5	0
1949	393	7	1.7	3
1950	404	6	1.4	6
1951	430	1	0.2	8
	2,247	58	2.5	18

In the series of 18 patients who delivered vaginally following previous cesarean section, there was no incidence of uterine rupture and neither maternal nor fetal mortality. The birth weight of these infants was from 6 pounds, 1 ounce to 9 pounds, 4 ounces. In this regard it is interesting to note that in 2 cases the previous section was done for fetopelvic disproportion and in each case the second infant was the heavier. Attention is called to the marked drop (1949) in the incidence of cesarean operations since the adoption of a more rational attitude toward secondary sections.

It is admitted that such a small series of cases has no particular statistical value, but it does compare favorably with the experience of the large clinics and should indicate a progressive trend and a promise for the future.

Summary and Conclusions

The current trend of liberalization of the indications for cesarean section is rapidly adding to the number of women who present the problem of pregnancy and delivery subsequent to surgery.

Conservative elements in our profession are demonstrating that vaginal delivery following cesarean section is in many cases a rational procedure.

Careful evaluation of each case rather than routine resection should free many women formerly condemned to multiple surgical procedures and give them an opportunity to demonstrate their ability to deliver vaginally.

The risk involved is admitted and an attempt is made to analyze the problem.

Proper selection of patients is emphasized. Methods for lowering mortality and morbidity are suggested.

A short summary of current statistics from the literature and my own practice is given.

A plea is made to discard the old dictum, "Once a cesarean section, always a section," to individualize each case, and to test the natural possibilities.

References

Avilés, V. M.: Tr. Internat. & Fourth Am. Cogress on Obst. & Gynec. (Supp. vol. AM. J. OBST. & GYNEC.) 61A: 309, 1951.
Burkons, H. F.: AM. J. OBST. & GYNEC. 42: 75, 1941.
Cody, M. L.: AM. J. OBST. & GYNEC. 62: 415, 1951.

Conti, E. A.: AM. J. OBST. & GYNEC. 60: 851, 1950.
Cosgrove, S. A.: Tr. Internat. & Fourth Am. Congress on Obst. & Gynec. (Supp. vol. AM. J. OBST. & GYNEC.) 61A: 307, 1951.
Duckering, F. A.: AM. J. OBST. & GYNEC. 51: 621, 1946.
Kistner, R. W.: AM. J. OBST. & GYNEC. 61: 109, 1951.
Low, D. M.: AM. J. OBST. & GYNEC. 61: 197, 1951.
Miles, Lee M.: Personal communication, 1952.
McLane, C. M.: AM. J. OBST. & GYNEC. 20: 650, 1930.
McLean, L. F., et al.: AM. J. OBST. & GYNEC. 60: 860, 1950.
Schmitz, H. E., and Towne, J. E.: Tr. Internat. & Fourth Am. Congress on Obst. & Gynec. (Supp. vol. AM J. OBST. & GYNEC.) 61A: 289, 1951.
Schmitz, H. E.: AM. J. OBST. & GYNEC. 61: 1232, 1951.

OCCULT TRAUMATIC RUPTURE OF THE UTERUS FOLLOWED BY SPONTANEOUS RUPTURE IN SUBSEQUENT PREGNANCY*

A Case Report

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ALL efforts and objectives in obstetrics are aimed primarily at the protection of the mother and the baby. With the recognition of obstetrics as a science and art basic principles of the mechanism of labor were the first to be studied. Disproportion, relative or absolute, with the classical picture of prolonged labor and risk of rupture is seldom seen today with the availability of modern obstetrical care. The answer to the problem of disproportion has been cesarean section.

Rupture of the uterus is not always associated with the problem of disproportion. Malpresentations managed by version and extraction have proved to be the greatest single cause of traumatic rupture of the uterus. Donnelly reports 39 cases of ruptured uteri in 101,127 deliveries and of these 12 were traumatic ruptures, and 8 were caused by version and extraction.

Rupture of the uterus may be classified as spontaneous, traumatic, and rupture of the scar of previous cesarean sections. The case reported represents a combination of an occult traumatic rupture of the uterus followed by a spontaneous rupture in a subsequent pregnancy.

The purpose of this case report is to point out that an occult rupture of the uterus can and does occur, but is probably reported as a spontaneous rupture in a following pregnancy. A diagnostic sign in the immediate puerperium, namely, shoulder pain due to pneumoperitoneum, if recognized, can establish a diagnosis of rupture of the uterus.

Case Report

Mrs. H. C., 31-year-old, gravida v, para iv, estimated date of confinement Feb. 11, 1952, was hospitalized at 9:15 A.M. on February 14. Approximately one-half hour prior to admission, her husband called stating that she was having persistent low abdominal pain, with vaginal bleeding. Past medical and surgical history was irrelevant.

The obstetrical history showed deliveries to have been at yearly intervals, the first three uncomplicated.

Fourth pregnancy and delivery: She was hospitalized at term on March 1, 1951, at 12:30 A.M., in early labor with occasional and mild contractions. Examination by the resident revealed a transverse presentation (?), presenting part floating, membranes intact. Fetal heart tones were regular in the right lower quadrant; the cervix was not dilated by rectal determination. Active labor began at 3:00 A.M., at which time rectal examination revealed 5 cm. dilatation. At 6:00 A.M. the membranes ruptured spontaneously, with prolapse of an arm in the vagina. The patient was taken to the delivery room and a sterile vaginal examination under cyclopropane anesthesia revealed the cervix completely dilated,

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Fort Worth, Feb. 13-14, 1953.

the membranes ruptured and the right scapula presenting, with prolapse of the right arm in the vagina. Version and extraction with Piper forceps on the aftercoming head were done under deep ether anesthesia. Delivery of a normal male infant that weighed 7 pounds, 12½ ounces was accomplished without difficulty. Manual removal of the placenta and exploration of the uterus were done. Brisk hemorrhage followed the manual procedure and the estimated blood loss was 600 c.c. The hemorrhage was controlled by forward angulation of the uterus. The cervix was inspected and a laceration at 12 o'clock was repaired. Mild shock was noted, with a drop in blood pressure from 140/80 to 100/70. Immediate postpartum therapy included 1,000 c.c. of whole blood. The postpartum course was characterized by abdominal distention and a persistent complaint of right shoulder pain, continuing up to the seventh postpartum day. There was no morbidity.

Recent history obtained in the fifth pregnancy revealed that for the past two to three weeks' prior to the onset of labor the patient had complained of remittent lower abdominal pain. A maternity corset had given relief. A tentative diagnosis of abruptio placentae was made. Ten minutes after admission the patient screamed in agonizing pain. She was taken to the operating room for immediate celiotomy with a provisional diagnosis of ruptured uterus. Immediate operation was possible because the operating room was set up for a scheduled cesarean section at 9 A.M. Anesthesia was started at 9:30 A.M., a midline incision of the abdomen at 9:33 A.M., blood started at 9:35 A.M. Upon opening the peritoneal cavity, which was tense and bluish, a tremendous gush of blood followed. It was impossible to estimate the amount of blood free in the abdominal cavity. At this time the patient was in deep shock and blood pressure and pulse were not obtained. A full-term anoxic female infant lying transversely to the long axis of the mother was extracted from the upper abdomen. The baby weighed 7 pounds, 12 ounces. The uterus was well contracted, the placenta being extruded from a large rent of the left lateral wall of the corpus of the uterus. Supravaginal hysterectomy was done. At this time blood was being administered in both arms and the patient's general condition was improved. A total of 2,500 c.c. of blood was given while the patient was on the operating table. There was no morbidity and the patient received another 500 c.c. of blood on the third postoperative day.

Follow-up on the baby reveals a definitely defective child. At 1 year of age the baby weighs approximately 14 pounds and cries continuously.

Pathological Report.—

Gross: The uterus weighed 1,150 grams and measured 16 by 15 by 11 cm. The serosa was smooth. An irregular laceration was present in the uterine wall extending downward from a point 6 cm. below the level of the fundus and involving the left lateral margin of the body of the uterus as well as of the lower uterine segment. The margins of the defect were covered by serosa which appears thickened and showed whitish discoloration. The serosa also extended over the inner aspect of the margins of the tear and could be demonstrated in the vicinity of the endometrium.

Microscopic: The myometrium showed hypertrophy of its individual fibers and presented a picture typical of the findings in pregnancy. Multiple sections were present from the margins of the defect and showed irregular thickening of the serosa with fibrosis, hyperemia, and leukocytic infiltration. The subserosal zone of the myometrium showed fibrous transformation and presented the picture of scar tissue with varying degrees of organization. In most of the sections, the serosa could be traced over the margin of the defect and in one of the sections it was separated from the endometrium only by a narrow zone of hyalinized material.

Pathological Comment.—The findings in the sections from the margin of the defect suggest previous incomplete disruption of the uterine wall with formation of a thin layer of scar tissue. It seems likely that this weakened area constituted the cause of the present rupture.

Comment

Certain predominant features of this case are noted. The fact that rupture of the uterus was not discovered during the course of manual exploration is unexplainable.

Fertility was not affected by a gross defect of the uterus.

The ultimate outcome of a well mother and live baby reflects the fortunate circumstances at hand, namely, rupture while in the hospital, the operating room set up for a previously scheduled cesarean section. Statistics in the group of cases quoted show there is an associated maternal mortality of 42.3 per cent and fetal mortality of 89 per cent.

The question arises as to the management of malpresentation by version and extraction or by cesarean section. It must be recognized that cesarean section itself carries a risk of subsequent rupture of the uterus. In the series quoted, out of 39 cases 13 were of previous cesarean section scar.

It has been my belief that there is a place in obstetrics for version and extraction. This experience, while not causing me to abandon this opinion, nevertheless emphasizes the extreme danger and limited use of version and extraction.

Summary and Conclusions

1. A case is reported of an occult, traumatic rupture of the uterus, with spontaneous rupture in a subsequent pregnancy.

2. Complete or incomplete rupture of the uterus following a major obstetrical procedure may escape detection, and may threaten a subsequent pregnancy.

3. Shoulder pain in the immediate puerperium should make one suspect a ruptured uterus.

4. Version and extraction as an obstetrical procedure must be accepted with full recognition of its potential dangers.

5. The fertility level was not affected by a major defect in the genital tract.

Reference

Donnelly, Joseph Patrick: Am. J. Surg. 82: 354, 1951.

ANTERIOR OCULAR OVARIAN GRAFTS IN THE RABBIT*

A Potential Tool in Endocrine Investigation for Clinician and Scientist†

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THE present study further exemplifies the usefulness of anterior ocular grafts, but more specifically how the physiology of ovarian tissue can be grossly studied by direct observation of transplants in the rabbit eye. Markee[1, 2] used the method for observing endometrial changes in homologous transplants in both rabbits and monkeys. Greene[3, 4, 5, 7] and Browning[6] have shown the value of the approach in a study of human embryonic and neoplastic tissue behavior. Only recently Stewart,[8] after utilizing anterior chambers of the eyes of rabbits for growing human placental tissue, presented conclusive evidence of the biologic activity of Langhans' cells.

Although Van Dooremal[9] first described the anterior ocular transfer technique in 1873, the first investigator to graft ovaries into animal eyes was Schochet,[10] who in 1920 inserted rat ovaries into homologous hosts and observed cyclic ovarian function. Later, May[11] similarly studied the development of rat ovaries and found cyclic changes including corpus luteum formation beginning 13 to 27 days after transplantation.

Pfeiffer[12, 13] studied the effects of intraocular rat ovarian grafts upon the development and maintenance of seminal vesicles and prostate in the castrate and noncastrate male rat.

Payne and Meyer[14] have demonstrated that homologous rat ovarian tissue is transplantable after growth in culture at 37° or storage at 10° C. They have further demonstrated that such ovarian tissue when transplanted into the anterior chamber of the rat eye is capable of producing estrogens as indicated by estrous type of vaginal smears.

Halbon[15] in 1933 suggested the use of ovarian transplants as a biologic test for pregnancy, assuming that rabbit ovaries transplanted into the anterior chamber of the eye would respond as they do in their normal location. Using 10 ocular ovarian grafts in 8 rabbits, Abramowicz and Zaleski[16] in 1935 performed 22 such tests using the urine of pregnant women. Two false negative reactions and several weakly positive reactions were recorded. Dworzak and Podleschka[17] reported follicular development in 22 out of 25 rabbit ovarian graft tests although actual follicular hemorrhage was reported in only 2 of

*Read before the Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Fort Worth, Feb. 13-14, 1953.

†Aided by grants to the General Research Funds, Baylor University College of Medicine, by the M. D. Anderson Foundation and by U. S. Public Health Service Cancer Teaching Grant 692-C-3.

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the tests. Similar experiments were carried out by Chamorro,[18] who tested 12 animals and had only one false negative reaction, and by others[19] who reported little success. May[20] reported follicle formation in response to pregnancy urine in 5 rabbits with anterior ocular ovarian grafts. Control urines from nonpregnant women failed to elicit the same response. Greene[21] completed a pilot experiment utilizing anterior chamber ovarian grafts in rabbits as a pregnancy test and reported initial "favorable results."

Dunham, Watts, and Adair,[22] in the hope of learning more of the genesis of ovarian tumors, transplanted newborn homologous rat ovaries into the anterior chambers of the eyes of 137 rats. Utilizing chorionic gonadotropin to stimulate the grafts, they observed a higher incidence of successful transplantation in the gonadectomized animals.

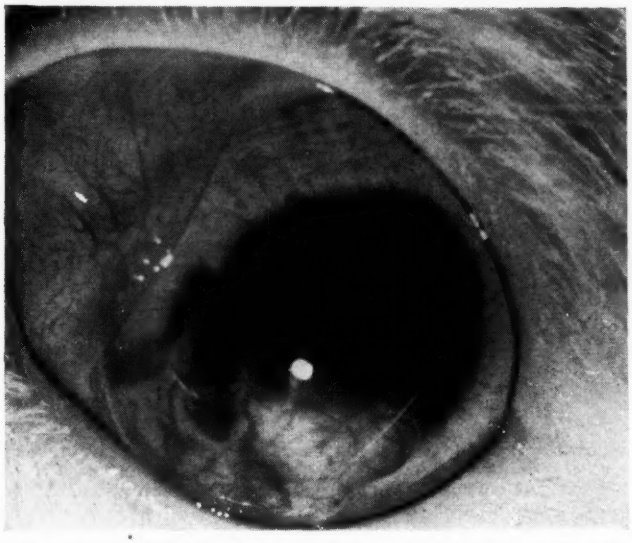

Fig. 1.—Gross appearance of transplanted ovarian tissue showing "rounding off" and vascularity. The corpus hemorrhagicum followed injection of human pregnancy urine.

Ward, Newton, and Gardner[23] found variant data in the literature on ovarian transplantability into the anterior ocular chamber. They attempted to evaluate transplantability of autologous (from one location to another within the same animal) and homologous (from one animal to another within the same species) rabbit ovarian tissue in 112 grafts. No statistically significant difference was observed in the incidence of growth of grafts in spayed and nonspayed females and castrate and noncastrate males.

Technique of Transplantation

The technique used in this study for transfer of homologous ovarian tissue to the anterior chamber of the rabbit eye is essentially the method described by Greene.[24] Anesthesia is accomplished by means of topical 1 per cent cocaine in physiological saline. Strict asepsis is necessary. A stab-wound incision is made at the corneoscleral junction at the most superior portion of the orbit with a straight-edged cataract knife. We have found either the Deutschmann or Graefe knife to be suitable. The blade is pushed deep into the anterior

chamber in one quick stroke and is immediately withdrawn. A spinal needle (about 15 gauge), which is modified by shortening the bevel, serves as the trocar. This is filled from the point end with a small portion (1 to 2 c.mm.) of ovary and then placed in the wound for a depth of 4 to 5 mm. The stylet of the needle is pushed down with the tissue being thus expelled into the anterior chamber. The tissue is then guided to the base of the anterior chamber by means of gentle downward pressure on the outer surface of the cornea. Any smooth, blunt instrument can be used for this purpose. The tissue should not be macerated. Originally it was felt that systemic penicillin would lower the incidence of inflammation in the eye, but Ward's[25] experience has not confirmed its value in mice. The use of albino rabbits is preferred because details of the transplant are more easily seen against a pink iris.

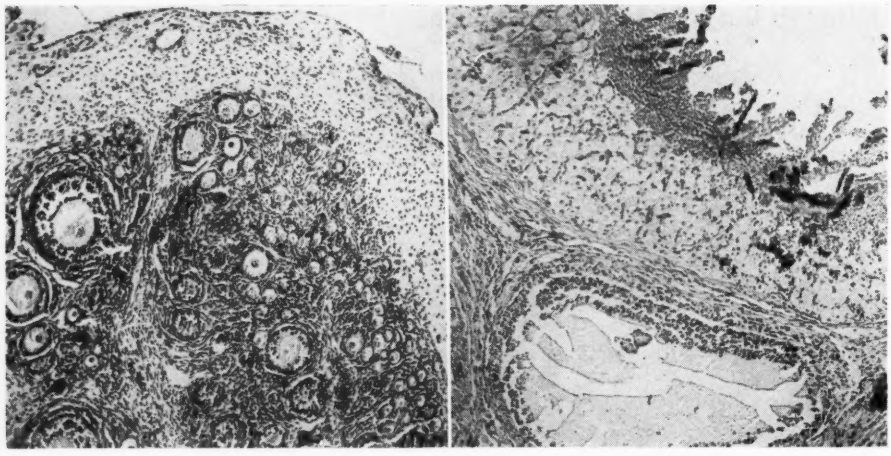

Fig. 2. Fig. 3.

Fig. 2.—Low power of viable ovarian transplant with follicles in various stages of development.

Fig. 3.—High power of corpus hemorrhagicum with luteinization and adjacent developing follicle after injection of human pregnancy urine.

Transplantability

At present, we have extended our former series[23] of 112 transplants, and now have a total of 134 transplants in 80 rabbits. Criteria of viability, as emphasized by Greene,[24] were the presence of vascularity, "rounding off," and increase in size of fragments (Fig. 1). These criteria were found reproducible and reliable. Follicular response to gonadotropic stimulation is also characteristic. Early in the study some animals were sacrificed for histological confirmation of viability (Figs. 2 and 3). Gross evidence of a "take" was usually apparent between the fifth and the fourteenth days after transplantation.

Four groups of host animals were studied with respect to transplantability: spayed females, nonspayed females, castrated males, and noncastrated males. Transplantation data are presented in Tables I and II.

The over-all transplantability rate was 105 "takes" in 134 grafts (78.4 per cent). Further analysis indicates that spaying and castrating do not significantly alter homologous transplantability. There also appears to be no

significant difference in incidence of transplantability between autologous and homologous grafts. In general, the incidence of transplantability is slightly higher in the female groups than in the male groups. Seemingly, the lack of significant difference present between spayed and nonspayed females would appear to place in question the validity of "Halsted's law of endocrine deficiency" (that a deficiency of a hormone produced by a gland facilitates successful transplantation of that particular gland), which Halsted,[26] Robertson[27] and others have postulated. Since their conclusions were based on the transfer of mature functioning glandular tissues, our results with relatively immature ovarian tissue probably offer no definite conflict with this concept.

TABLE I. AUTOLOGOUS TRANSPLANTS (DONOR AND HOST, SAME ANIMAL)

	4-WEEK DONORS		8-WEEK DONORS		12-WEEK DONORS		ALL AGE DONORS		
	GRAFTS	TAKES	GRAFTS	TAKES	GRAFTS	TAKES	GRAFTS	TAKES	
Spayed	4	3	4	3	20	16	28	22	(79%)
Nonspayed	4	3	4	4	4	3	12	10	(83%)

TABLE II. HOMOLOGOUS TRANSPLANTS (DONOR AND HOST, DIFFERENT ANIMALS)

	NEWBORN DONORS		4-WEEK DONORS		8-WEEK DONORS		12-WEEK DONORS		ALL AGE DONORS		
	GRAFTS	TAKES	GRAFTS	TAKES	GRAFTS	TAKES	GRAFTS	TAKES	GRAFTS	TAKES	
Castrate males	8	4	8	7	8	8	8	7	32	26	(81%)
Noncastrate males	8	7	8	3	8	5	13	11	37	26	(70%)
Spayed females	–	–	4	2	4	3	5	5	13	10	(77%)
Nonspayed females	–	–	4	4	4	4	4	3	12	11	(92%)

Gonadotropic Response

Our experience has shown that mature anterior ocular grafts of ovarian tissue are stimulated to production of hemorrhagic follicles by as little as 60 international units of chorionic gonadotropin per kilogram of animal weight, while, in other animals, only hyperemia may result from as much as 150 international units per kilogram. Thus the actual dosage needed to produce hemorrhagic follicles is quite variable.

In order to re-evaluate the usefulness of this technique as a biologic test for pregnancy, urine from pregnant women was given to host animals. In our first series, 50 tests were made using Friedman's procedure. Ten c.c. of filtered neutral urine, with a specific gravity of no less than 1.016, were injected by ear vein. Although none became positive later than 72 hours, the grafts tested were observed for 5 days. Only those considered to be viable according to criteria previously mentioned were used, and the production of gross hemorrhagic follicles alone was considered a positive reaction. We emphasize that those with hyperemia and simple follicles were not considered positive, although the reaction would seem to indicate a gonadotropic response of significance and worthy of further interpretation. The results are shown in Table III.

TABLE III. PREGNANCY TESTS, SERIES I

WEEKS PAST LAST MENSTRUAL PERIOD	7	9	10	11	12	13	14	15	16	20
Tests performed	1	4	4	2	11	2	9	9	7	1
Positive results	1	2	0	0	6	1	2	3	3	0

After assessing the results of this first series (18 positive out of 50 tests) it was felt that the grafts functioned poorly because of too early use after transfer, and/or immaturity of donor tissue. Consequently a second group of 54 tests were made three months or longer after transplantation. Forty-seven of the tests were in female hosts, while the remainder (7) were in male hosts. The majority of the animals were used more than once. The results are shown in Table IV.

TABLE IV. PREGNANCY TESTS, SERIES II

WEEKS PAST LAST MENSTRUAL PERIOD*	4	5	6	7	8	10	11	12	13	16	26	32	36
Tests performed	2	1	4	7	2	3	2	14	7	1	4	5	2
Positive results	2	1	4	7	2	3	2	10	5	1	2	3	2

*Repeat test ectopic pregnancy.

Of the 54 tests performed in this second group, 44 (81.5 per cent) were positive on the basis of the appearance of hemorrhagic follicles. Several of those considered negative showed hyperemia and clear follicles, indicating a gonadotropic response and for practical purposes could have been considered positive. Since the ovarian transplants could be directly observed before testing, hyperemia and clear follicles were known not to exist before the tests, thus making these reactions more significant. As is true in all biologic tests for pregnancy, the highest percentage of positives is seen in the first trimester. Hyperemia usually appeared not later than 8 hours after injection of urine, and gradual development of follicles could be observed to follow this, culminating in eventual formation of the corpus hemorrhagicum. In two animals, hemorrhagic follicles developed within 2 hours after urine injection; however, 36 to 48 hours was usual. None developed after 72 hours.

Normally, ovulation occurs in the rabbit only after copulation. The exact mechanism of this response has not been proved. In two instances, hemorrhagic follicles developed in transplants following copulation of the host animal. This, too, was observed by Dworzak and Podleschka.[17] This response of an ovary with no nerve supply further indicates indirect stimulation by way of the pituitary rather than by direct nervous stimulation.

Estrogenic Inhibition

Diminution of ovarian function, i.e., depression of follicular development by estrogens, has been reported[27-31] and ascribed to a direct or indirect action (via pituitary) on the ovaries. Our experience showed that relatively small doses of estrogens have a moderately inhibitory effect upon the responsiveness of the ovarian transplants to gonadotropic stimulation. Twenty-four hours after animals had received 5,000 I.U. of equine estrogens in sterile corn oil, 500 I.U. of chorionic gonadotropin was given intramuscularly. In a series of

25 such tests hemorrhagic follicular response occurred only 10 times (40 per cent). This dosage of gonadotropin would normally produce almost a 100 per cent response.

Another group of 10 animals were tested after 5,000 I.U. of estrogen had been given daily for 6 days. On the sixth day, simultaneously with the last dose of estrogen, 500 I.U. of chorionic gonadotropin was given. In the 10 animals so tested there was a complete suppression of all follicular activity, there being no gross follicles of any type and no hyperemia. Naturally, there cannot be a question of pituitary gland inhibition by estrogens as the explanation for the ovarian quiescence in this particular experiment since the ovarian stimulant (gonadotropic hormone) is being supplied by injection.

That actual chemical neutralization of gonadotropins by estrogens does not occur is suggested clinically in pregnant women under estrogen therapy whose urines remain Friedman positive. That the natural high level of estrogens during pregnancy fails to neutralize gonadotropins is additional evidence of the assumption that chemical neutralization does not occur. These facts, along with the results of this experiment, indicate that ovaries are made refractory to gonadotropic stimulation by the direct action of estrogens on the ovary.

Comment

Although the subject of heterologous grafts, i.e., human to rabbit, is not within the scope of the present discussion, their potential value in the study of endocrine physiology and anaplastic tissue behavior requires mentioning. Transplants of mature heterologous tissue will not survive, but heterologous transplants of embryonic and anaplastic tissue will survive. Application of the technique could reveal unknown facets of hormonal and malignant tissue activity. The possibilities should be fully explored by clinicians and basic scientists working as a closely wedded team.

Too often the published works of basic scientists are relegated to the shelves of medical libraries and forgotten, never becoming known to the clinician, and too often the scientist is unfamiliar with the problems confronting the clinician. If the chasm between the two could be bridged, the clinician and the patient would be materially benefited, and the efforts of the medical investigator would less often be in vain.

Summary

1. The transplantability of autologous and homologous ovarian tissue has been shown to be relatively high and the technique of transplantation simple.

2. The employment of ovarian transplants in a biologic test for gonadotropin (modified Friedman) has been shown to be feasible.

3. The practicability of visualizing continuously the inhibiting and stimulating effects of hormones on the transplanted rabbit ovary has been further demonstrated.

4. That ovarian tissue can be made completely refractory to gonadotropic stimulation by estrogens has been conclusively shown.

References

1. Markee, J. E., Wells, W. M., and Hinsey, J. C.: Anat. Rec. 64: 221, 1936.
2. Markee, J. E., Davis, J. H., and Hinsey, J. C.: Anat. Rec. 64: 231, 1936.
3. Greene, H. S. N.: Science 88: 357, 1938.
4. Greene, H. S. N.: Cancer Research 3: 809, 1943.
5. Greene, H. S. N., and Lund, P. K.: Cancer Research 4: 352, 1944.
6. Browning, H. C.: Cancer 2: 646, 1949.
7. Greene, H. S. N.: Cancer 5: 24, 1952.
8. Stewart, H. L., Jr.: Am. J. Obst. & Gynec. 61: 990, 1951.
9. Van Dooremal, J. C.: Von Graefes Arch. f. Ophth. 19: 359, 1873.
10. Schochet, S. S.: Surg., Gynec. & Obst. 31: 148, 1920.
11. May, R. M.: Arch. d'anat. micr. 35: 147, 1940.
12. Pfeiffer, C. A.: Am. J. Anat. 58: 195, 1936.
13. Pfeiffer, C. A.: Am. J. Physiol. 117: 672, 1936.
14. Payne, M. A., and Meyer, R. K.: Proc. Soc. Exper. Biol. & Med. 51: 188, 1942.
15. Halbon: Cited by Dworzak and Podleschka.[17]
16. Abramowicz, K. I., and Zaleski, W.: Zentralbl. f. Gynäk. 59: 634, 1935.
17. Dworzak, H., and Podleschka: Zentralbl. f. Gynäk. 60: 1928, 1936.
18. Chamorro, A.: Zentralbl. f. Gynäk. 60: 384, 1936.
19. Allan, E., and Priest, F. O.: Surg., Gynec. & Obst. 55: 553, 1932.
20. May, R. M.: Compt. rend. Soc. de biol. 138: 775, 1944.
21. Greene, H. S. N.: Personal communication re unpublished data, Oct. 9, 1950.
22. Dunham, L. J., Watts, R. M., and Adair, F. L.: Arch. Path. 32: 910, 1941.
23. Ward, J. E., Newton, B. L., and Gardner, H. L.: Proc. Soc. Exper. Biol. & Med. 77: 869, 1951.
24. Greene, H. S. N.: J. Exper. Med. 73: 461 and 475, 1941.
25. Ward, J. E.: Unpublished Master's Thesis, Dept. of Pathology, Baylor University College of Medicine, 1952.
26. Halsted, W. S.: J. Exper. Med. 11: 175, 1909.
27. Robertson, G. G.: Proc. Soc. Exper. Biol. & Med. 71: 542, 1949.
28. Kunde, M. M., D'Amour, F. E., Gustavson, R. G., and Carlson, A. J.: Proc. Soc. Exper. Biol. & Med. 28: 122, 1930.
29. Moore, C. R., and Price, D.: Am. J. Anat. 50: 13, 1932.
30. Allen, E., and Diddle, A. W.: Am. J. Obst. & Gynec. 29: 83, 1935.
31. Bullough, W. S.: J. Endocrinol. 3: 235, 1943.

Discussion

DR. J. W. VIEAUX, Dallas, Texas.—The work of Markee and the importance of his observations to the study of endometrial physiology through the use of intraocular transplants is familiar to most of us. We are probably less well acquainted, however, with the application of this technique to the investigation of ovarian function. That it has merit has been well emphasized by this paper.

Utilizing the gonadotrophic response as a test for pregnancy in this manner would certainly seem a simplification of the Friedman procedure. This, of course, assumes mastery of the transplantation technique. Other points of favor over the usual method are the elimination of error due to improper selection and isolation of rabbits and the fact that one rabbit should prove suitable for repeated tests. The latter has definite economic value. Although the accuracy in this small series of trials appears quite satisfactory, especially during the early weeks when a laboratory diagnosis of pregnancy is most needed, it would be interesting to know whether the use of blood serum as a source of gonadotropes would increase this accuracy to any extent. It would also be worth while to know whether or not involution of the hemorrhagic follicles might be stepped up through the administration of large doses of estrogens. This would be significant when rabbits are used for more than one test.

The study of estrogenic inhibition is of utmost importance in that it demonstrates a simple direct means by which the effects of the various sex hormones on ovarian tissue may be observed. This is in sharp contrast to the indirect information obtained through complicated blood and urine assays.

Original Communications

DISTURBANCE OF VITAMIN B_6 METABOLISM IN PREGNANCY*

III. Abnormal Vitamin B_6 Load Test

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IN THE presence of a vitamin B_6 deficiency an abnormal metabolite, xanthurenic acid (4-8 dihydroxyquinoline-2-carboxylic acid), is excreted in the urine in appreciable amounts following the oral administration of 10 Gm. dl-tryptophane.[1, 2, 3] Such an abnormality in tryptophane metabolism has recently been demonstrated in pregnant women.[4, 5, 6, 7] The present investigation was undertaken in order to find out whether evidence for the occurrence of a vitamin B_6 deficiency in pregnancy could be obtained by still another method. For this purpose use was made of a vitamin B_6 load test. In this test 25 mg. of pyridoxal hydrochloride is given by mouth and the amount of excreted 4-pyridoxic acid, the most important metabolic end product of pyridoxal, is measured in the urine. In the case of a vitamin B_6 deficiency the extra excretion of 4-pyridoxic acid is expected to be smaller than in normal subjects since more of the vitamin is retained by the tissues of the vitamin-depleted individual.

Material and Method

Sarett's[8] vitamin B_6 load test was used with some modifications. Twenty-five mg. of pyridoxal hydrochloride† were given in a small amount of water. The subjects' urine was collected for 8 hours. The period of 8 hours was chosen since almost all of the increased amount of formed 4-pyridoxic acid is excreted within this time. 4-pyridoxic acid was determined fluorometrically with the use of a fluorometer,‡ with the primary filter No. 5860 and secondary filters Nos. 4308 and 3389. All subjects were on a self-selected diet. In some of these the 8 hour urine specimens were examined for the presence of 4-pyridoxic acid on the day preceding the test. Only small amounts were found to be present. There was no significant difference in normal controls and pregnant women (Tables II and IV). In later experiments the pre-excretion values were therefore not determined. The values for 4-pyridoxic acid found following a test dose of vitamin B_6 included these small amounts of "endogenous" 4-pyridoxic acid. The series included 20 normal control subjects, 22 patients with miscellaneous diseases, and 56 pregnant women. Of these 56 pregnant women 42 had normal uncomplicated pregnancies while 14 showed the typical signs of toxemia. All pregnant women were tested in the maternity wards 1 to 2 days after delivery.

*Presented at a meeting of the Brooklyn Gynecological Society, March 18, 1953.

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†Pyridoxal hydrochloride and lactone of 4-pyridoxic acid were supplied through the courtesy of Dr. R. A. Peterman of Merck & Co., Inc., Rahway, N. J.

‡The fluorometer used was Model A made by the Farrand Optical Company, Inc., New York.

Results

Normal Controls.—As can be seen from Table I and Fig. 1, the 20 normal controls excreted between 9.25 and 13.40 mg. 4-pyridoxic acid with an average of 11.55 mg. Fifteen of these controls showed a pre-excretion value of 4-pyridoxic acid in 8 hours varying between 0.33 and 1.50 mg., with an average of .85 mg. (Table II).

TABLE I. NORMAL CONTROLS FOLLOWING TEST DOSE

NO.	NAME	SEX	AMOUNT OF URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	M. B.	F	170	9.25
2.	R. F.	F	510	9.56
3.	V. F.	F	270	10.00
4.	L. K.	F	400	10.50
5.	E. M.	F	920	10.58
6.	S. S.	F	150	11.03
7.	R. S.	F	710	11.05
8.	D. W.	M	540	11.34
9.	A. G.	M	385	11.55
10.	G. W.	F	300	11.60
11.	J. T.	M	405	11.74
12.	A. B.	F	500	11.80
13	E. B.	F	1,020	12.29
14.	M. G.	M	750	12.40
15.	D. P.	M	250	12.50
16.	C. S.	F	1,250	12.50
17.	D. G.	F	500	12.60
18.	C. T.	F	168	12.60
19.	H. M.	F	725	12.70
20.	M. W.	M	1,140	13.40
				Mean 11.55 (S.E. = ±0.25)

TABLE II. NORMAL CONTROLS BEFORE TEST DOSE

NO.	NAME	SEX	URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	R. F.	F	550	0.33
2.	L. K.	F	320	0.50
3.	R. S.	F	270	0.54
4.	E. B.	F	1,285	0.64
5.	V. K.	F	250	0.65
6.	D. G.	F	350	0.75
7.	G. W.	F	250	0.80
8.	C. S.	F	1,430	0.84
9.	D. W.	M	420	0.88
10.	S. S.	F	760	0.88
11.	C. T.	F	500	1.00
12.	A. B.	F	225	1.00
13.	E. M.	F	580	1.16
14.	M. G.	M	610	1.28
15.	H. M.	F	415	1.50
				Mean 0.85 (S.E. = ±0.07)

Patients With Various Diseases.—Twenty-two patients with various diseases excreted between 9.06 and 13.40 mg. with an average of 11.15 mg. (Table III and Fig. 1). There was no significant difference between this group and the normal controls.

Pregnancy at Term.—

A. Uncomplicated Pregnancy.—The pre-excretion values for 10 of these cases varied between 0.40 and 1.08 mg., with an average of 0.74 mg. (Table IV). They are not signicantly different from those of the normal control group. Following the test dose of 25 mg. pyridoxal hydrochloride excretion varied between 3.70 and 12.40 mg., average 8.84 mg. (Table V and Fig. 1). As compared with the normal control group this represents a highly significant decrease in the amount of excreted 4-pyridoxic acid ($p<0.001$).

B. Full-Term Pregnancies Complicated With Toxemia.—The excretion values of the 14 cases varied between 6.00 and 10.51 mg. with a mean of 8.53 mg. (Table VI and Fig. 1). As compared with the normal control group these women likewise showed a highly significant decrease in the excretion of 4-pyridoxic acid. There was, however, no significant difference between full-term pregnancies complicated with toxemia and those that had an uneventful course.

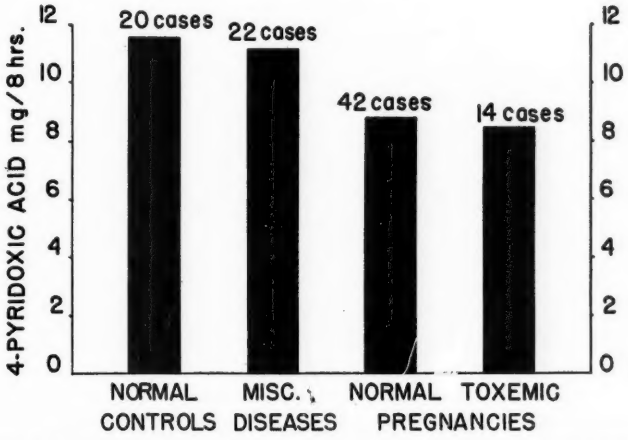

Fig. 1.—The urinary excretion of 4-pyridoxic acid for an 8 hour period following a test dose of 25 mg. pyridoxal hydrochloride in normal controls, patients with miscellaneous diseases, and in full-term pregnant women with and without toxemia.

Comment

The amounts of 4-pyridoxic acid excreted in the urine of normal controls preceding the test are in good agreement with figures given in the literature. In Sarett's experiments, for instance, individuals on a normal self-selected diet excreted between 0.6 and 11.1 mg. in 24 hours with an average of 3.4 mg.[8] Following the ingestion of 25 mg. pyridoxine hydrochloride Lossy, Goldsmith, and Sarett[9] found an average urinary excretion of 9.5 mg. 4-pyridoxic acid in the urine collected for 4 hours in 38 normal subjects. As expected, this figure is lower than our average of 11.55 mg. for an 8 hour period. Almost all of the excretion of 4-pyridoxic acid is apparently completed within 8 hours since in normal individuals the total amount of 4-pyridoxic acid in 24 hours averages 13 mg.[8]

In our series no significant difference in the excretion of 4-pyridoxic acid was seen in the groups of patients with various diseases although some of

TABLE III. MISCELLANEOUS PATIENTS FOLLOWING TEST DOSE

NO.	NAME	SEX	DIAGNOSIS	AMOUNT OF URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	G. S.	M	Fracture of sacrum	990	9.06
2.	C. B.	M	Subacute leukemia	190	9.40
3.	F. S.	M	Osteoarthritis	620	9.50
4.	J. C.	M	Prostatic hyperplasia	350	9.50
5.	A. R.	M	Myocardial infarction	310	10.00
6.	J. T.	M	Cirrhosis of liver Diabetes mellitus	830	10.25
7.	M. B.	M	Carcinoma of bladder	250	10.30
8.	F. Q.	M	Bronchopneumonia	500	10.30
9.	A. C.	M	Acute prostatitis	1,120	10.60
10.	C. E.	M	Carcinoma of prostate with bone metastasis	820	10.75
11.	M. T.	M	Acute rheumatic fever	500	10.80
12.	S. T.	M	Lobar pneumonia	500	11.00
13.	M. C.	M	Diffuse toxic goiter	300	11.10
14.	J. M.	M	Benign hyperplasia of prostate	450	11.30
15.	M. L.	F	Active rheumatic fever	930	11.75
16.	M. D.	F	Asthma, bronchial	113	11.75
17.	H. L.	M	Infected compound fracture	680	12.50
18.	D. C.	F	Decompensated hypertensive heart disease	260	12.68
19.	M. L.	F	Pneumonia	720	12.96
20.	B. M.	M	Myocardial infarct	560	12.99
21.	R. S.	F	Subacute pyelonephritis	500	13.30
22.	C. D.	M	Diabetic gangrene	500	13.40
					Mean 11.15 (S.E. = ±0.29)

$t = 1.2$

$p^1 < 0.3$

$p^1 > 0.2$

p^1 represents the chance occurrence of the difference observed between test and the "normal control" groups.

TABLE IV. NORMAL PREGNANCIES BEFORE TEST DOSE

NO.	NAME	AMOUNT OF URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	M. F.	630	0.40
2.	R. C.	400	0.50
3.	R. A.	400	0.50
4.	M. B.	250	0.60
5.	F. E.	250	0.80
6.	S. M.	400	0.80
7.	T. S.	240	0.84
8.	M. F.	350	0.90
9.	B. W.	670	0.95
10.	M. L.	900	1.08
			Mean 0.74 (S.E. = ±0.07)

$t^1 = 7.0$

$p^1 < 0.4$

$t^2 = 0.5$

p^1 represents the chance occurrence of the difference observed between test and the "normal control" groups.

these individuals had histories of inadequate food intakes. This is in good agreement with the findings of Lossy, Goldsmith, and Sarett.[9] These investigators examined the 4 hour urinary excretion of 4-pyridoxic acid following an

TABLE V. NORMAL PREGNANCIES AT TERM FOLLOWING TEST DOSE

NO.	NAME	AMOUNT OF URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	B. W.	500	3.70
2.	T. S.	300	4.23
3.	M. L.	210	4.62
4.	M. O.	260	6.24
5.	R. L.	360	6.75
6.	M. C.	500	6.75
7.	D. D.	420	6.80
8.	M. C.	690	7.00
9.	R. A.	440	7.04
10.	B. B.	900	7.31
11.	B. S.	265	7.95
12.	M. F.	390	8.00
13.	D. K.	1,000	8.15
14.	D. H.	600	8.16
15.	M. O.	1,100	8.20
16.	M. L.	400	8.27
17.	G. F.	520	8.32
18.	G. S.	585	8.33
19.	A. B.	525	8.40
20.	M. G.	1,630	8.40
21.	P. P.	455	8.42
22.	S. M.	320	8.50
23.	T. B.	300	8.60
24.	S. R.	1,040	8.60
25.	M. H.	400	8.80
26.	R. F.	325	9.26
27.	A. R.	300	9.30
28.	P. M.	960	9.66
29.	T. H.	310	9.73
30.	D. E.	1,250	10.00
31.	C. M.	605	10.58
32.	E. Q.	555	10.76
33.	M. K.	960	10.80
34.	M. E.	300	10.90
35.	R. B.	450	11.44
36.	L. S.	715	11.47
37.	J. C.	355	11.53
38.	S. B.	1,100	11.55
39.	F. F.	255	11.98
40.	A. P.	570	12.10
41.	L. B.	1,230	12.30
42.	R. G.	600	12.40
			Mean 8.84 (S.E. = ±0.33)

$t = 5.28$

$p^1 < 0.001$

p^1 represents the chance occurrence of the difference observed between test and the "normal control" groups.

oral test dose of 25 mg. pyridoxal hydrochloride in 6 groups of test subjects. These groups consisted of 38 controls, 6 miscellaneous hospital patients, 3 individuals on weighed diets low in B complex vitamins, 20 patients with signs of B complex deficiency, 5 patients with signs of thiamine deficiency, and 22 patients with diabetes mellitus. There was no appreciable difference between any of the abnormal groups and the normal controls.

In contrast to these findings is the distinct and highly significant decrease in the excretion of 4-pyridoxic acid in pregnant women at term, thus indicating an abnormal retention of the administrated vitamin B_6. Although the average excretion in women with uncomplicated pregnancies at term was

only 8.84 mg. as compared with 11.55 mg. for the control group, it should be noted that 17 out of these 42 women (40 per cent) excreted larger amounts than 9.25 mg., the lowest value found in the normal control group. This may be compared with previous findings using the tryptophane load test in pregnant women at term.[7] Among 14 normal controls following a test dose of dl-tryptophane between 0 and 30 mg. (average 14 mg.) of xanthurenic acid was excreted. One hundred pregnant women at term excreted between 0 and 813 mg., an average of 195 mg. xanthurenic acid. Among these 100 women only 4 (4 per cent) showed normal values (between 0 and 30 mg.). In comparison to the tryptophane load test, the vitamin B_6 load test is, therefore, apparently less sensitive in detecting a vitamin B_6 deficiency.

TABLE VI. TOXEMIAS AT TERM FOLLOWING TEST DOSE

NO.	NAME	AMOUNT OF URINE ML./8 HR.	4-PYRIDOXIC ACID MG./8 HR.
1.	M. S.	150	6.00
2.	V. P.	2,325	7.08
3.	M. R.	250	7.22
4.	M. S.	600	7.32
5.	K. G.	2,400	7.68
6.	C. V.	705	7.70
7.	M. K.	940	7.80
8.	L. M.	510	8.42
9.	C. S.	200	9.52
10.	G. A.	970	9.70
11.	Q. T.	1,100	9.70
12.	J. R.	415	10.37
13.	L. E.	800	10.40
14.	A. T.	320	10.51
			Mean 8.53 (S.E. = ±0.37)

$t^1 = 7.0$

$p^1 < 0.001$

$t^2 = 0.5$

$p^2 < 0.9$

p^1 represents the chance occurrence of the difference observed between test and the "normal control" groups.

p^2 represents the probability of chance occurrence observed between the "toxemia" and "normal pregnancy" groups.

An investigation similar to the present one has been previously carried out by Muziarelli and Piccioni,[10] who gave 30 mg. of pyridoxine intravenously to pregnant women and control subjects and estimated the amount of pyridoxine excreted in the urine. Between 12.6 and 16.2 per cent (average 14.65 per cent) of the injected vitamin B_6 was detected in the urine of 10 normal control subjects. In 10 women with uncomplicated pregnancies in the last trimester between 6.5 and 11 per cent (average 8.1 per cent) of the administered vitamin was found. Eighteen patients with toxemia of pregnancy in the last trimester did not significantly differ in their excretion since between 5.7 and 10.8 per cent (average 7.9 per cent) of the injected pyridoxine was found in the urine. Muziarelli and Piccioni used a colorimetric method for the quantitative determination of pyridoxine.[11, 12] This technique, however, is open to serious objections. Although the blue color reaction with the 2,6-dichloroquinone chlorimide used in this determination is not only given by pyridoxine but also by other substances, 4-pyridoxic acid does not react.

Since most of the vitamin B_6 not retained by the tissue is excreted in the urine as 4-pyridoxic acid[13] the small amounts of vitamin B_6 detected in the urine with the colorimetric method are readily explained. It is interesting to note that in spite of these technical objections our findings are in close agreement with those of the Italian investigators.

The results obtained present further evidence for the existence of a biochemically demonstrable disturbance in vitamin B_6 metabolism. It is probable that this disturbance is due to a deficiency in this important vitamin occasioned by the increased demands of the growing fetus. It has been shown by us[7] in both short- and long-term experiments that supplementation of a self-selected diet with small amounts of vitamin B_6 will readily rectify the abnormal tryptophane metabolism of pregnant women.

The vitamin B_6 load test indicated an equal degree of vitamin B_6 deficiency in both women with normal pregnancies and those with toxemia. This is in some contrast to previous findings with the tryptophane load test, since the average excretion of xanthurenic acid was higher in toxemic patients.[6] It is, however, doubtful whether much significance should be attached to this difference. Not only has it been shown in the experimental animal that the amount of excreted xanthurenic acid is not proportional to the severity of the deficiency,[14] but it was also seen that no correlation could be established in individual cases between the severity of toxemia and the quantitative abnormality of the tryptophane load test.[6]

Summary

Further evidence for the existence of a vitamin B_6 deficiency in pregnancy was established with the help of a vitamin B_6 load test. In this test the urinary excretion of 4-pyridoxic acid, the main metabolic end product of vitamin B_6, was measured for an 8 hour period following the ingestion of 25 mg. pyridoxal hydrochloride. Full-term normal and toxemic pregnant women were found to excrete smaller amounts of 4-pyridoxic acid than either normal controls or patients with various diseases. Thus pregnant women retain administered vitamin B_6 to a significantly larger extent than do control subjects.

References

1. Greenberg, L. D., Bohr, D. F., McGrath, H., and Rinehart, J. F.: Arch. Biochem. **21**: 237, 1949.
2. Glazer, H. S., Mueller, J. F., Thompson, C., Hawkins, V. R., and Vilter, R. W.: Arch. Biochem. **33**: 243, 1951.
3. Wachstein, M., and Gudaitis, A.: Am. J. Clin. Path. **22**: 652, 1952.
4. Vandelli, I.: Acta vitaminol. **5**: 55, 1951.
5. Sprince, H., Lowy, R. S., Folsome, C. E., and Behrman, J.: Am. J. Obst. & Gynec. **62**: 84, 1951.
6. Wachstein, M., and Gudaitis, A.: J. Lab. & Clin. Med. **40**: 550, 1952.
7. Wachstein, M., and Gudaitis, A.: J. Lab. & Clin. Med. **42**: 98, 1953.
8. Sarett, H. P.: J. Biol. Chem. **189**: 769, 1951.
9. Lossy, F. T., Goldsmith, G. A., and Sarett, H. P.: J. Nutrition **45**: 213, 1951.
10. Muziarelli, A., and Piccioni, V.: Clin. Obstet. **51**: 189, 1949.
11. Scudi, J. V., Koones, H. F., and Keresztesy, J. C.: Proc. Soc. Exper. Biol. & Med. **43**: 118, 1940.
12. Scudi, J. V., Unna, K., and Antopol, W.: J. Biol. Chem. **135**: 371, 1940.
13. Rabinowitz, J. C., and Snell, E. E.: Proc. Soc. Exper. Biol. & Med. **70**: 235, 1949.
14 Cerecedo, L., and DeRenzo, E.: Arch. Biochem. **29**: 273, 1950.

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THE IMPORTANCE OF GRAVITY IN DELAYED LIGATION OF THE UMBILICAL CORD*

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NUMEROUS papers have been written on the value to the newborn of delayed ligation of the umbilical cord following delivery.[1, 4, 5, 7, 8, 11, 12] Very few, however, have stressed the importance of gravity in the transference of blood from the placenta and its vessels to the infant and vice versa. Landau[1] suspended the placenta following delivery by cesarean section until all pulsations of the cord had stopped.

Impetus for this present study was gained from a presentation of a paper by S. R. M. Reynolds[2] before the Brooklyn Gynecological Society on the x-ray study of the fetal circulation of sheep. In this study,[2a] using sheep fetuses, he and his associates showed that when ventilation is begun there is a considerable fall in both pulmonary arterial and aortic pressures, the pulmonary circulation becomes more rapid, and the circulating pulmonary blood volume increases. As the lungs inflate, the pulmonary vascular bed increases in size, blood rushes in to fill it, and there is diminished venous return to the left side of the heart. Aeration of the blood causes an extensive redistribution of blood throughout the organism. Moreover, in addition to these changes within the fetus at the time of birth, data were obtained to show that blood normally flows within the vessels of the umbilical cord under the influence of a small difference in pressure between its two ends. Thus the action of gravity at the time of birth may determine the direction of blood flow and affect its volume in any given time.[2b] Reynolds[2] also described an unpublished study by Mary Gunther of the University College Hospital, London, England, in which she showed that, in the human being, once the cord stopped pulsating the flow of blood from placenta to infant is dependent upon gravity when the uterus is not contracted.

The purpose of this study was to confirm these reports and to establish a practical procedure designed to effect rapid exchange of blood from the placenta to the baby. Moreover, while these figures were being compiled it was decided to evaluate the general health and progress of these infants as compared with those of controls and, finally, if the results came up to expectations, to make delayed ligation of the cord so practical and rational that the procedure would appeal to the majority of physicians practicing obstetrics.

*Read at a meeting of the Brooklyn Gynecological Society, April 15, 1953.

Method

Ninety-four infants were studied in three groups. Group A consisted of 23 infants who were weighed on a scale placed six inches above the level of the mother while still attached by the cord to the placenta in utero. Group B consisted of 24 infants weighed with the scale at the mother's level while still attached to the placenta. Group C contained 47 infants that were weighed six, twelve, or more inches below the level of the mother while attached to the placenta.

The scale was a metric platform Detecto scale which was placed on a series of four removable boxes each six inches high, resting in turn on a movable base. The level of the infant could be altered readily by either removing or adding these boxes. It was assumed that 1 gram in weight change was approximately equivalent to 1 c.c. of blood.

No special precautions were taken in the conduct of labor or delivery. Previous studies were carried out with the use of a minimum of sedation with a general anesthetic[4] or no analgesia or anesthesia[9] whatsoever. At the Brooklyn Hospital the majority of labors are conducted under Demerol-scopolamine analgesia with or without Nembutal or seconal, and for the actual delivery cyclopropane, pudendal block, or spinal anesthesia is given. In this series, 82 patients received cyclopropane, 2 had spinal anesthesia, while 10 were delivered under local anesthesia. During the course of this study many infants could not be included for the following reasons: asphyxia neonatorum, short cord, tight loop of cord around the neck, or several loops of cord around the neck, fetal distress just prior to and after delivery, postpartum hemorrhage, or blood from the vagina falling on the scale.

Upon delivery of the infant, the scale was moved into position and the initial weight was rapidly recorded. Mucus was aspirated with a rubber bulb syringe and the infant "encouraged" to cry. Simultaneously 1 c.c. of Pitocin was given to the mother intramuscularly. If apnea existed for a minute despite aspiration and mechanical stimulation, the weighing was concluded and the baby turned over immediately for resuscitation. Pulsations of the cord were noted. If any appreciable gain of weight was noted in two or three minutes, the cord was ligated. Rarely was the weighing continued for more than four or five minutes because the mother was usually under general anesthesia. The first signs of placental separation were noted and if the infant did not gain appreciably in one to two minutes, the placenta was expressed, if separated, and held high for an additional one to two minutes. Some of the combined results are recorded in the tables. Failure to express the placenta shortly after separation occasionally resulted in excessive blood loss, because at times the blood is pocketed by the membranes and is not seen until the placenta is delivered. Most placentas will separate within three minutes when an oxytocic agent is used immediately after delivery.

Results

Group A (Above the level of the mother).—

These infants gained an average of only 8 grams in an average time of 3.4 minutes. While the cord was pulsating strongly, the infants, with few exceptions, gained well "uphill," one infant having gained 60 grams in only two minutes. However, if the cord was pulsating weakly or not at all, the weight was either stationary or it actually decreased. There were 15 infants in this group which demonstrated the importance of gravity once the cord either pulsated weakly or stopped entirely. Some of these gained weight while the cord pulsated well; they lost some or all of the gain when the cord stopped and

they regained the lost weight plus an additional amount of blood when either the baby was lowered or the placenta was delivered and held well above the level of the infant. This is shown in Table I, and in Fig. 1.

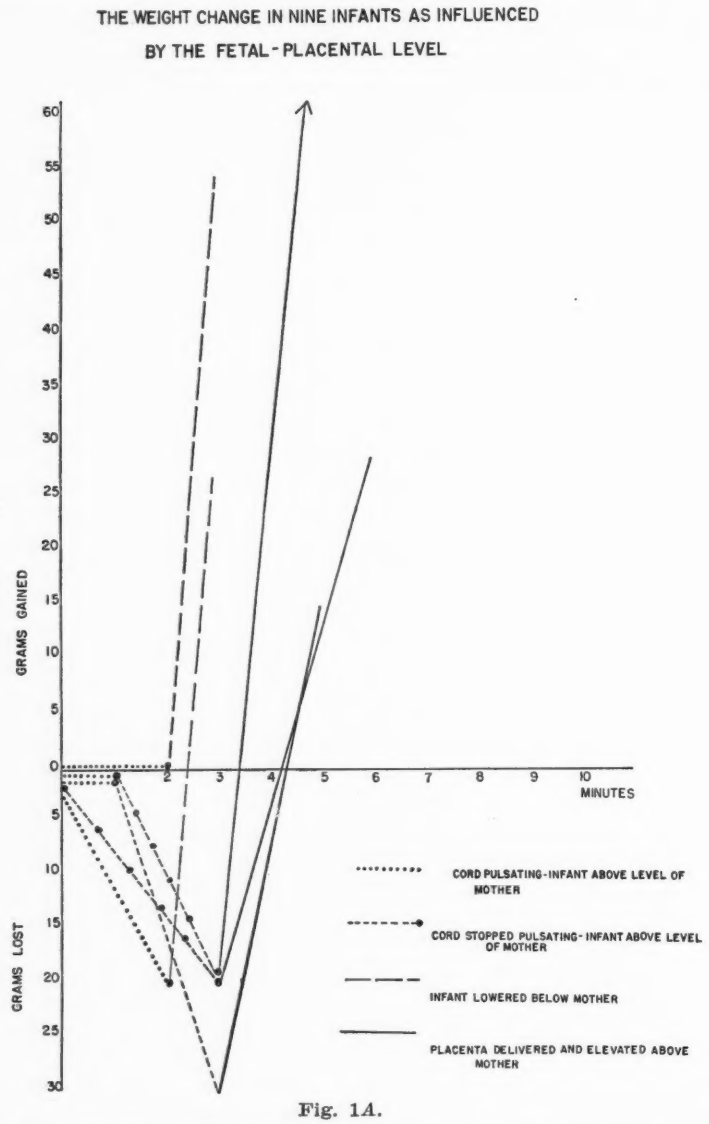

Fig. 1A.

Figs. 1*A* and 1*B*.—This graph was divided into two parts containing 5 and 4 cases, respectively, for the sake of clarity. They demonstrate that, although there might be some gain of weight with the infant held above the mother while the cord is pulsating, there is a definite drop in weight when the cord stops pulsating. In all cases, this drop in weight is quickly overcome when the infant is lowered or the placenta is delivered and held above the level of the infant.

Group B (Scale level with the mother).—

These babies gained an average of 33 grams in an average time of 3.1 minutes. As in the previous group, if the placenta separated after a short interval it was expressed and elevated for one or two minutes. This added to the total gain. However, it was not included in the reported average gain of 33 grams for this part of the series. These figures are shown in Table II.

Group C (Below the level of the mother).—

The largest number of infants were in this group for several reasons. First, three different levels below the mother were utilized: six inches, twelve inches, and as low as the length of the cord would permit. Second, this level was somewhat favored when it was seen how much more the babies gained. These infants increased their weights by an average of 41 grams in an average time of 3.3 minutes. This did not include the additional gain created by expressing the placenta and holding it high. Some of these cases are recorded in Table III.

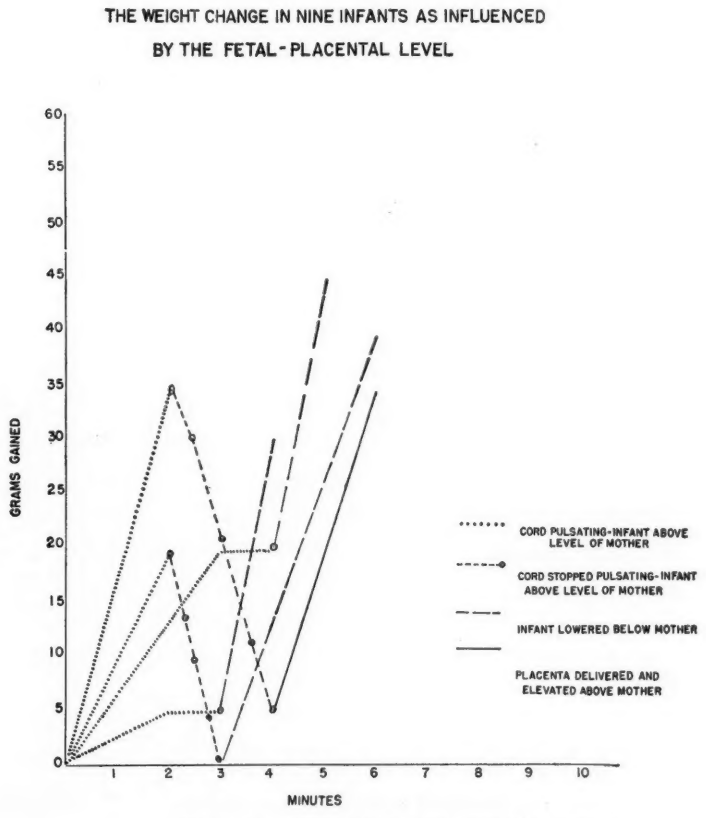

Fig. 1*B*.—(*For legend see opposite page.*)

Comparison Between Infants in Groups A, B, and C and Control Group.—A comparison was made in the nursery between these infants and 78 controls whose cords were clamped immediately in an attempt to determine the advantages or disadvantages of delayed ligation. The following observations were made:

Jaundice: Only one case was noted in the D. L. (Delayed Ligation) group while two were noted in the controls.

Activity: (This includes crying, arm and leg movements, twisting and sucking.) All were considered good in the D. L. group, but in the controls five were considered fair, one was poor, and the remainder good.

TABLE I. SCALES SIX INCHES ABOVE THE LEVEL OF THE MOTHER

PATIENT	INFANT WEIGHT IN GRAMS	PULSATIONS OF CORD		INFANT LOWERED	PLACENTA ELEVATED	REMARKS
		STRONG	WEAK OR STOPPED			
1. M.R.	3,575	+20 Gm. in 3 min.	After 4 min.	+25 Gm. in 1 min.		
2. A. Q.	2,805	+10 Gm. in 3 min.	After 1 min.	No change		Cord traumatized, around body once. Loop slipped over, but distended and collapsed loop of cord noted
3. A. B.	3,260	+40 Gm. in 3 min.	After 3 min.	−20 Gm. in 2 min.	+40 Gm. in 3 min.	Cord around body once. Loop, loose, slipped over head
4. L. L.	3,305	+5 Gm. in 2 min.	After 3 min.	+35 Gm. in 1 min.		
5. G. P.	2,690	0 Gm. in 1 min.	After 1 min.	+55 Gm. in 2 min.		
6. M. S.	4,220	0 Gm. in 3 min.	Did not stop in time allotted	+40 Gm. in 3 min.		Rh negative. No antibodies. Cord pulsating throughout
7. A. N.	3,515	+20 Gm. in 2 min.	After 2 min. −20 Gm. in 1 min.	+30 Gm. in 3 min.		Rh negative. No antibodies
8. E. K.	3,430	−20 Gm. in 2 min.	After 2 min. no change	+50 Gm. in 2 min.		Total gain of 30 Gm.
9. S. Q.	3,320	+35 Gm. in 2 min.	After 2 min. −30 Gm. in 2 min.		+30 Gm. in 2 min.	
10. M. P.	2,840		After 1 min. −30 Gm. in 2 min.		+45 Gm. in 2 min.	Cord around neck once. Loose, slipped over
11. T. C.	3,525	+40 Gm. in 3 min.	After 4 min. −10 Gm. in 1 min.		No change in 2 min.	No change. This was 8 min. after delivery
12. J. L.	3,220		0 Gm. in 2 min.		+30 Gm. in 2 min.	Cord resting on edge of scale with compression of vessels by its own weight. Gentle stripping
13. S.	3,810		−20 Gm. in 3 min.		After 4 min. +50 Gm. in 3 min.	
14. A. C.	3,675	0 Gm. in 3 min. Moderate pulsations			After 3 min. +60 Gm. in 3 min.	
15. M. H.	3,650		After 1 min. −20 Gm. in 2 min.		After 3 min. +105 Gm. in 3 min.	Actual gain of 85 Gm.

All deliveries were at term.

Respirations of infants were spontaneous and immediate except Case 4 where there was a delay of one minute.

Cases 6 and 13 delivered under pudendal block; remainder were delivered under cyclopropane.

General Well-Being: In the D. L. group two were considered fair, two were poor and the remainder good. In the controls seven were fair, four were poor, and the balance good.

Complications: In the D. L. group one infant was cyanotic for more than three hours after birth, six vomited after the first 48 hours, and six had non-

TABLE II. SCALES AT THE LEVEL OF THE MOTHER

PATIENT	INFANT WEIGHT IN GRAMS	PULSATIONS OF CORD		PLACENTA ELEVATED	REMARKS
		STRONG	WEAK OR STOPPED		
1. M. C.	3,040	+35 Gm. in 1 min.		After 2 min. +10 Gm. in 2 min.	Total gain 45 Gm. in 4 min.
2. J. M.	3,435	+20 Gm. in 2 min.	After 2 min. −10 Gm. in 2 min.	After 6 min. +35 Gm. in 1 min.	Total gain 45 Gm. in 7 min., mostly after placenta was expressed
3. M. O.	3,060	+30 Gm. in 2 min.	After 2 min. No change in 1 min.	After 3 min. +10 Gm. in 2 min.	Total gain 40 Gm. in 5 min.
4. A. S.	3,670	+40 Gm. in 2 min.	After 3 min. no change	After 4 min. +25 Gm. in 1 min.	Total gain of 65 gm. in 5 min.
5. M. H.	2,900	+30 Gm. in 1 min.		After 3 min. +10 Gm. in 1 min.	Total gain of 40 Gm. in 4 min.
6. D. T.	3,275	+15 Gm. in 1 min.	After 2 min. +30 Gm. in 1 min.		Total gain of 45 Gm. in 3 min.

All deliveries were at term except Case 3 at 37 weeks' gestation.
Infant respirations delayed one minute in Case 2; manual rotation from left occipto-posterior to occipitoanterior with low forceps extraction.
Case 6 was delivered under low spinal; remainder were delivered under cyclopropane.

pustular skin rashes. However, in the controls eleven were cyanotic for more than three hours after delivery, twelve vomited after the first 48 hours, and nine had skin rashes, four of which were pustular. Two infants from this group had poor weight gain.

Red Blood Count and Hemoglobin: On the average the hemoglobin was 3.4 Gm. higher and the red blood cell count approximately 500,000 cells higher in the D. L. group than in the controls. Since so much variation existed in blood gained by the infant, dependent on the level used, the above counts were naturally higher in those infants that gained 50 or more Gm. of blood. This would approximate one-sixth of their entire blood volume.

Observations

From this study certain observations and comments can be made:

1. While the umbilical cord pulsates vigorously blood will flow from the placenta to the infant in varying amounts, favoring the infant who is held below the mother's level.

2. When the cord stops pulsating or pulsates weakly, the transference of blood from the placental vessels and cord to the infant and vice versa is almost entirely dependent upon gravity.

3. Holding the infant well below the level of the mother for three minutes following delivery or until the cord collapses (whichever comes first) will add from 50 to 75 per cent of the available blood in the placental vessels and cord to the infant's blood volume (Table III). If the placenta separates while waiting, expressing it and holding it elevated for two to three minutes will accomplish the same end more effectively.

TABLE III. SCALES SIX OR TWELVE INCHES BELOW THE LEVEL OF THE MOTHER

PATIENT	INFANT WEIGHT IN GRAMS	PULSATIONS OF CORD		PLACENTA ELEVATED	REMARKS
		STRONG	WEAK OR STOPPED		
1. B. F.	2,905	+35 Gm. in 1 min.	After 1 min. +20 Gm. in 1 min.		This infant was 12 inches below level of mother and gained 55 Gm. in 2 min.
2. D. A.	3,995	+60 Gm. in 2 min. Cord pulsations only moderate	After 2 min. +15 Gm. in 1 min.		Total of 75 Gm. in 3 min. Infant 12 inches below level of mother
3. B. B.	3,055		After 1 min. +60 Gm. in 3 min.		Infant 12 inches below level of mother. Total 60 Gm. in 3 min.
4. M. Z.	2,930		After 1 min. +50 Gm. in 2 min.		Total of 50 Gm. in 3 min. Infant 12 inches below level of mother; cord once around neck slipped over
5. S. A.	4,155	Moderate +15 Gm. in 1 min.		After 4 min. +60 Gm. in 2 min.	Infant 6 inches below mother. Total 75 Gm. in 6 min., most of this in 2 min. following elevation of placenta
6. M. B.	4,475	+35 Gm. in 2 min.	After 3 min. +10 Gm. in 1 min.		Infant 12 inches below mother. Total gain 45 Gm. in 3 min. Partial compression of cord in vagina by placenta. Distended and collapsed loops noted
7. E. E.	3,750		After 1 min. +30 Gm. in 1 min.	After 3 min. +90 Gm. in 2 min.	Infant 6 inches below mother. Rh negative, no titer. Total gain 120 Gm. in 5 min.
8. M. R.	4,000	Cord pulsations mod. +150 Gm. in 3 min.			Cord around neck once slipped over. Scales 12 inches below level of mother. The greatest gain in entire series

All respirations were spontaneous except in Case 3 where there was a delay of 1 minute. All deliveries were at term.

4. With the cord pulsating well, a contraction of the uterus around the separated placenta will frequently transfer much of the available placental blood to the infant.

5. Any trauma to the cord (loops around the neck which are slipped over the head or its resting on the edge of the scale) will hinder the flow of blood. This was frequently seen and was evidenced by intermittent collapsed and dilated segments of cord at the point of trauma. Gently stripping the cord tends to overcome this temporary obstruction which is probably due to a spasm of the vessels.

6. An infant with a lusty cry tends to gain more readily than the apneic or sluggish one. This would be another point in favor of reducing the amount of analgesic drugs used in labor in conjunction with a general anesthetic.

7. Holding an infant above the mother's level after delivery by cesarean section might result in blood loss toward the placenta if the cord is not pulsating vigorously. This practice should therefore be avoided to prevent possible dangers to the infant.

8. There is no increase in clinical jaundice due to delayed ligation. These infants moreover show fewer complications and seem to exhibit more activity and enjoy better general health than those in the control series. In those infants who acquired 50 or more Gm. of blood by delayed ligation, the hemoglobin was on the average 3.4 Gm. and the red cell count 500,000 more than the controls.

Comment

Extensive studies have been made by numerous observers stressing the advantages of delayed ligation of the umbilical cord.[1, 4, 5, 8, 9, 11, 12] In premature births, delayed ligation of the cord is of particular value because a higher percentage of the total blood volume is disseminated in the cord and placenta.[3] Transfusion as a means of combating shock after a traumatic delivery may be accomplished by delayed ligation.[4] Ballentine found that the cord continues to pulsate from seven to thirty minutes after delivery. Our experience has been somewhat different. When Pitocin is given directly after delivery, most cords stop pulsating shortly after the placenta separates, usually within three to five minutes. An important factor is the area of the cord that is palpated. Pulsations cease gradually from the vulva downward, so that they can be felt near the umbilicus of the infant several minutes after they have stopped or become very weak at the middle of the cord. Ballentine also confirmed the work of Haselhorst[5] when he showed that 55 per cent of the available blood flowed into the infant from the placenta in the first minute and 84 per cent in five minutes. He found no correlation between the weight of the baby, length of the cord, the time the cord pulsated, and the amount of blood gained.

Our average time for delayed ligation was three to five minutes and we could not duplicate the high percentage of blood obtained by the infant in the first minute as shown by Haselhorst and Ballentine. Perhaps the scales used accounted for the difference. It took us from 10 to 20 seconds to obtain the first weight after delivery.

Landau describes the advantages of delayed ligation in cesarean section to prevent a syndrome which he calls hematogenic shock. In this symptom complex the infants leave the operating room in apparently good condition. Later they develop cyanosis, respiratory distress with dyspnea, air hunger, and costal retraction with a weak rapid pulse. They fade rapidly and die in terminal convulsions in about 18 to 24 hours. Potter[6] has studied autopsies on infants with this syndrome and discovered no apparent cause for the external hydrocephalus which was fairly constantly found except for the type of delivery (cesarean). Landau suspended the placenta for 6 to 10 minutes after delivery by section in 87 babies and did not observe any fetal deaths from this syndrome.

Frischkorn and Rucker[7] found the red blood count is greater by 584,481 red cells per cubic millimeter in infants whose cords are tied after they have ceased to pulsate than in those whose cords are ligated while still pulsating. DeMarsh[8] found a difference of 3 to 4 Gm. of hemoglobin and 700,000 to 1,000,000 red blood cells. He noted no truly significant difference in the icteric in-

dex in his series. Using the dye method of Gibson and Evans he found the average total blood volume of human infants allowed to retrieve their placental blood at birth to be about 361 c.c., or 11.8 per cent of the body weight, between birth and the third day of life.[10] The hematocrit value of this blood was 60 per cent and the plasma volume was 138 c.c., or 4.5 per cent of the body weight. Clamping the cord immediately, the average total blood volume was only 301 c.c., or 9.6 per cent of the body weight. The hematocrit value was 51 per cent. The plasma volume, 140 c.c., or 4.5 per cent of the body weight, was not altered. He also showed that blood drawn from the infant's heel 20 to 75 minutes after birth had significantly higher red corpuscle and hemoglobin values than blood drawn from the umbilical cord at birth.

It is possible that the spleen plays a part in bringing on this polycythemia at birth. Windle[11] states that the common practice of promptly clamping the cord at birth should be condemned because it is comparable to submitting the infant to a rather severe hemorrhage. It appears to result in increased erythropoiesis, which is reflected in an increase in circulating reticulocytes. It is evident from their recent studies that deprivation of the newborn infant of his placental blood may lead to iron deficiency in infancy.[12] Fullerton[13] and Stearns and McKinley[14] have stated that the principal iron reserve of the newborn infant is in the circulating hemoglobin rather than the tissues. Iron liberated during blood destruction is stored in the tissue and utilized as needed for hemoglobin formation. The amount of iron lost in this way is enough to lower the hemoglobin in a 4-month-old infant from 12 to 9.3 Gm. per 100 c.c. of blood. He quotes Engel[15] as stating that premature infants whose cords were tied promptly at birth had a 50 per cent greater mortality than those whose cords were tied late.

From the above evidence as well as from our own results, the importance of practicing delayed cord ligation in all infants is evident. This is particularly true in premature and cesarean infants. Stevenson[16] has stated that the infant does not need this extra blood and does well without it. This might be compared to the healthy blood donor who can safely give 750 c.c. of blood without ill effects. But the anemic or weakened adult could not do the same. Then why expect the average infant to do so when that is what immediate clamping of the cord constitutes? It may be supposed that when Nature's plan was evolved and women had their babies in an upright, squatting position, they were not expected to have a busy obstetrician or practitioner deliver the human infants in lithotomy position and a reasonable time was intended to elapse before the placenta was separated from the infant. It is true that many advances have been made in medicine in the past one hundred years but immediate clamping of the cord is certainly not one of them.

However, it would not be practical to wait from ten to thirty minutes before ligating the average umbilical cord as was done in the previous experiments,[1, 4, 5, 8] because most deliveries today are carried out under inhalation anesthesia. However, except in cases of emergency or probable erythroblastosis fetalis physicians can safely delay the ligation of the cord from three to five minutes. By holding the infant well below the level of the mother or by

delivering the placenta if it should separate very quickly and holding it up for one to two minutes especially until after the cord stops pulsating and collapses, the infant can be assured of at least two-thirds of the available blood in the placenta and its vessels. During this time the infant is kept warm and the mucus aspirated by the assistant or nurse in attendance. The doctor's efforts will be rewarded by a healthier, ruddier infant who has a better chance for survival.

Summary and Conclusions

1. The literature on delayed ligation of the umbilical cord has been reviewed and discussed.

2. Delayed ligation can be advantageously practiced despite the routine use of analgesia and anesthesia.

3. The importance of gravity in transporting blood from placenta to infant has been shown. Holding the infant with an unligated umbilical cord above the mother's level might result in loss of blood to the placenta especially if the cord has stopped pulsating.

4. A suggestion is made to place this procedure on a practical basis in the hope of making it more universally accepted.

5. Infants whose umbilical cords are not clamped immediately seem to enjoy better health on the average while in the nursery.

We wish to express our appreciation to Dr. Louis M. Hellman, Professor of Obstetrics and Gynecology, State University of New York College of Medicine at New York City, who reviewed the paper and made valuable suggestions; to Dr. S. R. M. Reynolds of the Carnegie Institution of Washington, who inspired this study and contributed so much to its physiological background; to Dr. J. Thornton Wallace, Director of the Department of Obstetrics and Gynecology of Brooklyn Hospital, for his encouragement and for providing the necessary equipment and facilities of the Hospital.

References

1. Landau, D. B.: J. Pediat. **36**: 421, 1950.
2. Reynolds, S. R. M.: Personal communications, 1952.
2a. Reynolds, S. R. M., et al.: J. Physiol. **118**: 2, 1952.
2b. Reynolds, S. R. M., Light, F. G., Ardram, G. A., and Pritchard, M. M. S.: Bull. Johns Hopkins Hosp. **91**: 83, 1952.
3. Smith, C. A.: Physiology of Newborn Infant, Springfield, Ill., 1945, Charles C Thomas.
4. Ballentine, G. N.: Pennsylvania M. J. **50**: 726, 1947.
5. Haselhorst, G.: Ztschr. f. Geburtsh. u. Gynäk. **98**: 103, 1930.
6. Potter, E.: Illinois M. J. **83**: 100, 1943.
7. Frischkorn, H. B., and Rucker, M. P.: Am. J. Obst. & Gynec. **38**: 592, 1939.
8. DeMarsh, Q. B.: Am. J. Dis. Child. **75**: 860, 1948.
9. DeMarsh, Q. B.: J. A. M. A. **116**: 2568, 1941.
10. DeMarsh, Q. B.: Am. J. Dis. Child. **63**: 1123, 942.
11. Windle, W. F.: J. Pediat. **18**: 538, 1941.
12. Wilson, E. E.: Am. J. Dis. Child. **62**: 320, 1941.
13. Fullerton, H. W.: Arch. Dis. Childhood **12**: 91, 1937.
14. Stearns, G., and McKinley, J. B.: J. Nutrition **13**: 143, 1937.
15. Engel, G.: Zentralbl. f. Gynäk. **9**: 721, 1885.
16. Stevenson, S. S.: J. Pediat. **40**: pp. 64, 1952.

THE EFFECT OF TRAVEL UPON THE INTERRUPTION OF PREGNANCY*

An Analysis of 1,917 Cases With Minimum Journeys of 300 Miles

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ALTHOUGH travel during pregnancy has been discussed before,[1-4] the literature lacks a substantial report to prove or disprove any resultant harmful effect upon pregnancy. While some doctors let their patients make short trips during gestation, a considerable number do not allow their patients to take trips because of the possibility of abortion, premature labor, or other maternal-fetal complications. Most obstetricians have little occasion to observe the effects of travel on their patients, since the general population as a whole is more or less static, and parents are usually settled permanently by the time a pregnancy is considered.

During World War II large numbers of people were moving about and, quite possibly, a substantial number of pregnant women. However, due to gasoline rationing, priorities on civilian transportation, and absence of husbands overseas, their movements were sharply curtailed. When the present national emergency arose in 1950, large groups of men were again uprooted from their relatively permanent positions. This time there were no restrictions on traveling, and they took their families along or were joined by them at a later date. This presented us with the opportunity of observing a large group of women who were traveling during pregnancy. Therefore, the purpose of this paper is to present a large enough series for statistical evaluation to either prove or disprove the harmful effect of travel on gestation.

Material

The data comprising this report were collected during the twelve-month period from Dec. 31, 1951, to January 1, 1953, at two separate Air Force hospitals in Alabama and Mississippi. Most of the patients were Caucasians in good health who had adequate prenatal care or received good prenatal care subsequently. Due to the rapid turnover of personnel at training bases, a large group of women were continually traveling to keep up with their husbands' movements. Little or no restriction could be imposed upon these women in regard to their traveling, since they refused to remain in a strange place even temporarily, when their husbands moved to a new base.

*The views expressed are those of the authors and do not necessarily reflect those of the Air Force.

No case in this series is counted twice, even though a woman may have made several long journeys from time to time. As far as possible only the patient's first trip is recorded, although subsequent ones may have been much longer. No patient in this series journeyed less than a minimum of 300 miles at one time. This minimum journey was arbitrarily set in order to give the woman an adequate exposure to travel; since a car averaging 50 miles per hour would take six hours to cover that distance, and a train averaging 60 miles per hour would take five hours. Long journeys were counted when a layover did not exceed two or three days. If longer breaks occurred, for one reason or another, the second or third part of the trip was not included in the patient's data.

Threatened abortion in this series was recorded whenever any bloody vaginal discharge occurred, whether it was accompanied by abdominal cramps or not. Abortion, as used in this series, is the interruption of pregnancy before the twenty-eighth week of gestation, and prematurity is based on birth weights of 1,000 to 2,500 grams.

No attempt was made to include ocean voyages from the Far East or Europe, as a large enough group could not be assembled. However, one point should be mentioned about these cases. A large number complained of moderate to severe motion sickness, so we felt that they should be given Dramamine or some other suitable drug prophylactically during their voyage. There were two exceptionally long and rough trips taken by automobile by a surprisingly large number of patients between the United States and Alaska or Newfoundland. The longer airplane flights were between the Far East, England, Europe, the Middle East, South America, and the United States.

A minimum follow-up period of four weeks was kept on all patients from the end of their journeys. Those women who went to other bases were given index cards, which were filled out by their physicians and returned to us after their four-week follow-up period was concluded.

Analysis of Data

A total of 1,917 women were seen who traveled a minimum of 300 miles or more during pregnancy. The total data are shown in Table I, which gives the number of patients in each six-week period of gestation and the number of miles traveled. At the bottom of each column and at the right of each column, the total number of patients for each group is recorded. Also at the bottom of each column and at the right of each column, the number of abortions and threatened abortions are recorded for each group, so that one can note whether more abortions or threatened abortions occurred with long or short trips and the period of pregnancy when they occurred. A total of 64 threatened abortions occurred in this group of 1,917 cases, giving an over-all incidence of 3.3 per cent; and 75 abortions occurred, giving an over-all incidence of 3.9 per cent. However, if one uses the interruption of pregnancy prior to 28 weeks of gestation as the criterion of abortions and threatened abortion, the total number of cases becomes 1,773 with 64 threatened abortions (an incidence of 3.6 per cent) and 75 abortions (an incidence of 4.2 per cent). In order to determine whether or not the longer trips were associated with any more threatened abortions and abortions than the shorter trips, one has only to divide the total number of patients traveling before 28 weeks of gestation into the figures in the right-hand column. Thus the incidence for threatened abortions runs approximately between 4.5 per cent and 2 per cent, while the

incidence of abortions runs approximately between 5 per cent and 2 per cent. Therefore, the length of the journey apparently has no increased effect upon the incidence of threatened abortions or abortions. In correlating the incidence of threatened abortions and abortions to the duration of pregnancy at the time of the journey, one finds the incidence greater during the first 12 weeks of gestation rather than from 12 to 28 weeks, as would be expected normally. To be more specific, the incidence of threatened abortions from 0 to 6 weeks' gestation and from 6 to 12 weeks' gestation is approximately 6 per cent each and thereafter drops to 3 per cent and less; while the incidence of abortions from 0 to 6 weeks' gestation is 6.3 per cent, and from 6 to 12 weeks' gestation is 10 per cent, dropping thereafter to approximately 1 per cent.

TABLE I. SUMMARY OF 1,917 CASES OF PREGNANT WOMEN WHO TRAVELED A MINIMUM OF 300 MILES AT ONE TIME SHOWING THE OVER-ALL RELATIONSHIP BETWEEN ABORTIONS AND THREATENED ABORTIONS TO BOTH THE DISTANCE TRAVELED AND THE DURATION OF PREGNANCY AT THE TIME OF THE JOURNEY

LENGTH OF TRIP IN MILES	DURATION OF PREGNANCY IN WEEKS AT TIME OF JOURNEY							TOTAL CASES	THREATENED ABORTIONS	ABORTIONS
	0-6	6-12	12-18	18-24	24-30	30-36	36-40			
300-600	24	101	106	84	58	38	11	422	13	17
600-1,000	54	107	105	74	56	25	12	433	17	17
1,000-1,500	27	117	116	84	37	23	9	413	17	19
1,500-2,000	26	59	56	39	24	5	2	211	6	8
2,000-4,000	39	112	92	75	50	12	5	385	10	13
4,000 plus	4	13	18	11	5	1	1	53	1	1
Total cases	174	509	493	367	230	104	40	1,917		
Theatened abortions	10	31	17	4	2				64	
Abortions	11	51	7	6						75

Eastman[5] gives the incidence of spontaneous abortion as approximately 10 per cent of all pregnancies. Since the incidence of abortion is considerably less in this series, we feel justified in stating that the etiological factor initiating the onset of abortions and threatened abortions in these cases was probably not the journeys. This will be better substantiated later in the paper.

In this series the occurrence of premature labor, happening within a four-week follow-up period after the completed journey, was extremely low. Using 1,000 to 2,500 grams or 2.2 to 5.5 pounds as the criterion for prematurity, only 3 cases of premature labor occurred. These were:

CASE 1.—A white gravida ii, para i, abortions 0, made an 800-mile trip by car at 34 weeks' gestation and delivered a 5 pound, 3 ounce infant at 38 weeks.

CASE 2.—A white gravida 1, para 0, abortions 0, took a 1,200-mile car trip at 32 weeks' gestation and delivered a 3 pound, 8 ounce infant at 34 weeks' gestation.

CASE 3.—A white gravida i para 0, abortion 0, made a 3,200-mile journey by car at 32 weeks' gestation, went into premature labor on the last day of the trip, and delivered a 5 pound, 7 ounce baby.

Of the women who delivered term babies, only 2 went into labor within 48 hours of the termination of their journeys.

There were certain minor complications arising in these women which caused physical discomfort but did not result in any serious outcome. Since

these are subjective complaints, the figures are probably inaccurate because some women will complain unnecessarily, while others who had mild to moderate discomfort will state that they felt fine. A large number of women said they became fatigued, but experienced no other discomfort during their journeys. There were 7 who complained of extreme pain in the lower back, and 11 had swollen ankles or legs. Pain in the lower abdomen or abdominal cramps were experienced by 33 women, 11 of whom were in the first trimester of pregnancy, 14 of whom were in the second trimester, and 8 of whom were in the third trimester of pregnancy. Motion sickness or severe nausea and vomiting occurred in 52 women, all but 6 of whom were less than five months pregnant at the time of the trip. The mode of travel in these cases was 29 by automobile, 12 by train, and 11 by airplane.

At this point brief mention may be made of the relationship of previous abortions to subsequent abortions in travel during pregnancy. There was a total of 236 patients in this series who had one or more previous abortions. In this group there were 10 cases of threatened abortion, an incidence of 4.2 per cent; and 13 cases of abortion, an incidence of 5.5 per cent.

TABLE II. AUTOMOBILE TRAVEL IN 1,526 CASES, SHOWING THE NUMBER OF MILES TRAVELED, THE DURATION OF PREGNANCY AT THE TIME OF THE JOURNEY, AND THE INCIDENCE OF ABORTIONS AND THREATENED ABORTIONS

LENGTH OF TRIP IN MILES	DURATION OF PREGNANCY IN WEEKS AT TIME OF JOURNEY						
	0-6	6-12	12-18	18-24	24-30	30-36	36-40
300-600	24	94	98	79	53	35	10
600-1,000	42	86	81	57	44	21	10
1,000-1,500	25	89	90	54	26	17	7
1,500-2,000	18	43	43	28	12	4	2
2,000-4,000	34	86	69	53	34	8	4
4,000 plus	4	9	18	9	4	1	1
Total cases	147	407	399	280	173	86	34
Threatened abortions	10	26	14	4	1		
Abortions	10	46	7	4			

TABLE III. TRAIN TRAVEL IN 244 CASES, SHOWING THE NUMBER OF MILES TRAVELED, THE DURATION OF PREGNANCY AT THE TIME OF THE JOURNEY, AND THE INCIDENCE OF ABORTIONS AND THREATENED ABORTIONS

LENGTH OF TRIP IN MILES	DURATION OF PREGNANCY IN WEEKS AT TIME OF JOURNEY						
	0-6	6-12	12-18	18-24	24-30	30-36	36-40
300-600		4	8	4	4	3	
600-1,000	10	14	16	8	8	3	1
1,000-1,500	1	18	22	23	4	4	
1,500-2,000	5	9	11	10	5		
2,000-4,000	4	13	12	10	6	2	1
4,000 plus		1					
Total cases	20	59	69	55	27	12	2
Threatened abortions		5	1				
Abortions	1	3					

Table II presents 1,526 patients who traveled by automobile during pregnancy, the number of miles traveled, the duration of pregnancy at the time of the journey, and the incidence of abortion and threatened abortion. Likewise, Table III shows 244 patients who traveled by train, and

Table IV gives 147 patients who traveled by airplane. Thus the individual mode of travel in the three instances of car, train, and airplane is presented to determine if any one factor had any increased effect upon threatened abortion or abortion. As can be seen from these three tables, the type of travel had no great effect upon the pregnancy. The incidence of abortion was higher in car trips, being 4.7 per cent before the twenty-eighth week of gestation, as compared to 1.7 per cent in train trips and 2.9 per cent in airplane trips.

TABLE IV. AIRPLANE TRAVEL IN 147 CASES, SHOWING THE NUMBER OF MILES TRAVELED, THE DURATION OF PREGNANCY AT THE TIME OF THE JOURNEY, AND THE INCIDENCE OF ABORTIONS AND THREATENED ABORTIONS

LENGTH OF TRIP IN MILES	DURATION OF PREGNANCY IN WEEKS AT TIME OF JOURNEY						
	0-6	6-12	12-18	18-24	24-30	30-36	36-40
300-600		3		1	1		1
600-1,000	2	7	8	9	4	1	1
1,000-1,500	1	10	4	7	7	2	2
1,500-2,000	3	7	2	1	7	1	
2,000-4,000	1	13	11	12	10	2	
4,000 plus		3		2	1		
Total cases	7	43	25	32	30	6	4
Threatened abortions			2		1		
Abortions		2		2			

Table V shows the relationship of the time interval between the termination of the journey and the onset of symptoms in the 75 abortions and the 64 threatened abortions in this series. Travel probably exerts little causative effect on initiating the symptoms of abortion or threatened abortion beyond two weeks after the termination of the trip. If this is true, then approximately one-half of the abortions and threatened abortions in this series can be discounted, and certainly all cases occurring beyond four weeks can be discounted as far as their relationship to the journey is concerned. While no one can argue the possible causal relationship within the first or second week after the end of the journey, any symptoms occurring after this period of time are open to question. Diddle[1] goes as far as to state that symptoms must follow trauma to pregnancy within 24 to 48 hours for a causal relationship to exist.

Another interesting observation was the incidence of abortion that occurred during travel in pregnancy when threatened abortion existed prior to the journey. There were 32 patients who had threatened abortion prior to their trips; 8 had bleeding within one week of their journeys and of these, 4 aborted. The other 24 cases were about equally distributed between 2 and 12 weeks from the time of their symptoms to the time of their journeys, and none of these patients aborted.

One maternal death occurred in this series. This was the case of a 23-year-old white gravida iii, para 0, abortion 2, who traveled approximately 1,000 miles by car at 16 weeks' gestation. She aborted one week after the end of the trip. Her past history revealed that she had had subacute bacterial endocarditis. She developed adynamic ileus, heart failure, and anuria and died one week after aborting, despite all possible treatment. The autopsy report showed far-advanced cirrhosis of the liver, myocarditis, and pericarditis.

TABLE V. THE RELATIONSHIP OF THE TIME INTERVAL BETWEEN THE TERMINATION OF THE JOURNEY AND THE ONSET OF SYMPTOMS IN 75 ABORTIONS AND 64 THREATENED ABORTIONS

LENGTH OF TRIP IN MILES		INTERVAL IN DAYS FROM END OF TRIP TO ONSET OF SYMPTOMS					
		0-7	7-14	14-21	21-28	28-35	OVER 6 WEEKS
300 to 600	Threatened abortion	6	2	3			2
	Aborted	7	1	2	2		5
600 to 1,000	Threatened abortion	7	7		2	1	1
	Aborted	3	6	2	3		2
1,000 to 1,500	Threatened abortion	8	3	2		3	1
	Aborted	8	2	5	1	1	2
1,500 to 2,000	Threatened abortion	2	2	1			1
	Aborted	1	2	2		1	2
2,000 to 4,000	Threatened abortion	4	2	1	1	2	
	Aborted	5	2		1		5
4,000 plus	Threatened abortion	1					
	Aborted						1
Total threatened abortions		28	16	7	3	5	5
Total abortions		24	13	11	7	3	17

Comment

Since we had little control over the movement of pregnant patients, an excellent opportunity arose to observe the effects of travel upon pregnancy. As more data were collected, we found that the incidence of complications arising during or after long journeys was no more than would be expected to occur normally in a similar group of patients who did no traveling. However, it is probably inadvisable to allow patients to make long journeys in less than 4 to 6 weeks after a threatened abortion.

Patients who make long trips should be given their prenatal charts so that they may present doctors with their records should complications occur while in transit. They were also advised on how to go about locating physicians should the necessity for their services arise during the journey. If nausea and vomiting of pregnancy were present prior to the trip, mild sedatives were prescribed, and Dramamine was taken along by patients making airplane flights for use in the event of rough weather. Although some controversy exists over pregnant women flying, no patient in our series experienced any more serious side effect than motion sickness. As far as lack of oxygen is concerned, this factor remains a theoretical objection due to the relatively low altitudes at which the majority of commercial aircraft make short flights, while long flights are made in pressurized cabins. The only restriction placed upon automobile trips was that the patient should not travel any further once she became fatigued without stopping for rest. A surprisingly large number of women drove 600 to 800 miles a day without stopping, while others experienced marked fatigue during or after a 300 or 400 mile journey. Traveling by train seemed to be just as tiring to the patients as other modes of travel due to the constant jerking and swaying motion.

Summary and Conclusions

1. A total of 1,917 patients were observed who traveled a minimum of 300 miles at one time during pregnancy. Of this number, 1,526 traveled by automobile, 244 traveled by train, and 147 traveled by airplane.

2. A total of 75 abortions and 64 threatened abortions occurred in this series with a minimum follow-up period of four weeks after the termination of the journey. This gives a 4.2 per cent incidence of abortions occurring before 28 weeks' gestation, which is well below the generally accepted incidence of 10 per cent for spontaneous abortion.

3. The incidence of premature labor and the onset of labor in term patients following journeys was negligible in this study.

4. No one type of transportation apparently had any advantage over any other type in preventing abortion, threatened abortion, or minor complications. Also, the longer journeys were associated with no more complications than the shorter ones.

5. The occurrence of an abortion in a previous pregnancy did not increase the risk of abortion to women who traveled. There were 236 patients who had had a previous abortion; and, of these, 13 aborted in this series, giving an incidence of 5.5 per cent in this group of women.

6. Of 32 women who had experienced threatened abortion prior to their journeys during the present pregnancy, only 4 aborted, but all 4 of these had symptoms within one week of their trips. Therefore, it is probably advisable to delay traveling at least 4 to 6 weeks after all symptoms of threatened abortion have ceased.

7. It is doubtful if any symptoms of abortion or threatened abortion arising in pregnant women within 2 weeks after their trips, and certainly not after 4 weeks, can be blamed on the journeys. In either case the number of abortions and threatened abortions in this series, supposedly attributable to traveling, is substantially reduced by this limiting time factor.

8. Simple precautions and common sense should guide one in making pregnant women more comfortable when they travel. We do not believe that travel during pregnancy carries any additional hazards to gestation than would normally occur in nontraveling pregnant women.

References

1. Diddle, A. W.: Texas State J. Med. **44**: 520, 1948.
2. Diddle, A. W.: Am. J. Obst. & Gynec. **48**: 354, 1944.
3. Beach, W. B.: Am. J. Obst. & Gynec. **54**: 1054, 1947.
4. Whittingham, H. E.: Practitioner **166**: 165, 1951.
5. Eastman, N. J.: Williams Obstetrics, ed. 10 New York, 1950, Appleton-Century-Crofts, Inc., p. 477.

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THE USE OF A MIXTURE OF MORPHINE AND N-ALLYLNORMORPHINE* AS AN ANALGESIC

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MORPHINE has been popular as a potent and superior analgesic agent. According to Wolff, Hardy, and Goodell,[1] its efficacy depends on (1) an elevation of pain threshold, (2) production of sleep, and (3) the alteration of psychologic reaction, replacing fear by relaxation. However, the deleterious effect of morphine on respiration, circulation, and gastrointestinal activity has precluded its use in geriatric, pediatric, and obstetric patients. Recently, experimental and clinical studies have demonstrated the effectiveness of n-allylnormorphine* in the prevention and treatment of morphine depressant effects.[2-7] Consequently, three studies were undertaken: (1) to find the appropriate dose of n-allylnormorphine which when mixed with morphine minimized its side effects, (2) to assess the analgesic properties of this mixture of morphine and n-allylnormorphine, and (3) to determine the degree of respiratory depression in the newborn when the morphine-n-allylnormorphine mixture is administered to the laboring mother.

Study 1. The Clinical Effect of Adding Various Concentrations of N-Allylnormorphine to a Fixed Dose of Morphine.—

The aim of this study was to find the appropriate dosage of n-allylnormorphine which when mixed with morphine maximally offset its depressant effects. Patients in labor who were having a sufficient degree of pain to require sedation were utilized for the study. In an initial group of 20 patients a selected, fixed dose of 15 mg. of morphine sulfate was administered intravenously. Three subsequent groups of patients were injected with either 5, 10, or 15 mg. of n-allylnormorphine combined with the fixed dose of 15 mg. of morphine. Respiratory activity was assessed on the basis of the respiratory rate. Unfortunately, no spirometric observations were undertaken. Pulse rate and blood pressure determinations were checked prior to the injection of the drugs and every ten minutes thereafter. The results of the study are summarized in Table I.

Respiratory depression with decreased pulse rate and blood pressure was observed in those patients who received the morphine alone. Within a few minutes after injection, the n-allylnormorphine-morphine mixtures transiently stimulated respiration both in depth and rate in all patients. The addition of 5 mg. of the n-allylnormorphine to the fixed dose of morphine decreased the intensity of the respiratory depression. Respiratory changes of a minor order were encountered in those patients who received 10 or 15 mg. of n-allylnor-

*The n-allylnormorphine was supplied by Dr. Elmer Alpert of the Department of Medical Research of Merck & Co., Inc., Rahway, N. J., and is now available as Nalline.

TABLE I. CLINICAL EFFECT OF ADDING VARIOUS CONCENTRATIONS OF N-ALLYLNORMORPHINE TO A FIXED DOSE OF MORPHINE

NO. OF PATIENTS	DOSE (MG.)		MAXIMUM CHANGE IN RESPIRATORY RATE/ MIN.	MAXIMUM CHANGES		MAXIMUM CHANGE IN PULSE RATE (AVE.*)
	MORPHINE SULFATE	N-ALLYL.		SYSTOLIC BLOOD PRESSURE (AVE.*)	DIASTOLIC BLOOD PRESSURE (AVE.*)	
20	15	0	−10 to −2 range Ave. −5.2	−22	−13	−14
10	15	5	−7 to +3 range Ave. −3.6	−9	−5	−6
10	15	10	−7 to +5 range Ave. −1.9	−8	−3	−3
10	15	15	−8 to +10 range Ave. −2.1	−5	+2	+4

*Average to nearest whole number.

TABLE II. CLINICAL EFFECTS FOLLOWING ADMINISTRATION OF EQUAL PARTS OF MORPHINE AND N-ALLYLNORMORPHINE

NO. OF PATIENTS	EQUAL DOSE MORPHINE SULFATE AND N-ALLYL.	EFFECT		DURATION OF EFFECT	CHANGE IN RESPIRATORY RATE	CHANGE IN BLOOD PRESSURE		CHANGE IN PULSE RATE
		HYPNOTIC	ANALGESIC			SYSTOLIC	DIASTOLIC	
25	5 to 20 mg. range Ave. 10.8 mg.	2+ to 4+ Ave. 3.5+	1+ to 4+ Ave. 3+	50 min. to 505 min. Ave. 192 min.	−8 to +10 range Ave. −0.3	−30 to +20 Ave.* −3	−20 to +16 Ave.* −2	−24 to +28 range Ave.* +4

*Average to nearest whole number.

morphine with the morphine injection. The effect on blood pressure and pulse rate was variable, but in those cases where the larger doses of n-allylnormorphine were employed less severe changes occurred.

Study 2. The Analgesic Properties of a Mixture Containing Equal Concentrations of Morphine and N-Allylnormorphine.—

A pilot study was conducted on 25 obstetric patients who were in active labor and required sedation. Fifteen mg. of n-allylnormorphine was mixed with 15 mg. of morphine and 0.4 mg. of scopolamine hydrochloride. Fractions of this mixture were administered intravenously to each patient until an adequate degree of hypnosis and analgesia was achieved. A slight effect was rated as 1 plus, a moderate effect as either 2 plus or 3 plus, and a maximum effect as 4 plus. On the analgesia study chart was recorded the time of each drug administration, degree and duration of hypnosis and analgesia, blood pressure readings, pulse rate, respiratory rate, and the obstetric progress of the patient. The observations of this study are summarized in Table II.

A high degree of pain relief was achieved in all of the patients studied with minimal effect on the respiratory or circulatory system. The patient's labor progress was considered to have advanced at a normal rate.

Study 3. The Effect on the Respiratory Activity of the Newborn When a Mixture of Morphine and N-Allylnormorphine Is Administered to the Laboring Mother.—

The patients of this study are the offspring of the patients in Study 2. There were 26 newborn infants (this group included one set of twins). An infant was considered depressed if he did not breathe or cry spontaneously within the first 2 minutes after birth or if he required any resuscitative measures. All newborn infants in this series were born alive. One infant exhibited respiratory depression, the remainder breathed and cried spontaneously. The one depressed child in the group was the firstborn of the twins, was apneic at birth, but responded quickly to intermittent positive pressure oxygen resuscitation. The second of the twins was delivered by version and breech extraction, and cried spontaneously. Eighteen of the 25 mothers were delivered under regional anesthesia; deep (third-plane) ether anesthesia was administered on one occasion for the delivery of the second twin, light (first-plane) cyclopropane anesthesia was utilized for the delivery of the remainder of the patients.

Further Observations

Since the completion of the preliminary study the mixture of morphine and n-allylnormorphine has been employed in different situations and by various routes. A mixture of 10 mg. each of morphine and n-allylnormorphine has been administered to patients in labor, half intravenously and half intramuscularly. Occasionally, the entire dose was injected either intramuscularly or intravenously.

Proportionately smaller doses of the morphine-n-allylnormorphine mixture have been utilized for preoperative medication in pediatric and geriatric cases.

In addition, the mixture has been employed for postoperative pain relief and for painful medical conditions where intense sedation without respiratory depression was desired.

Comment

The objections which may be raised to this report are that there are a small number of cases in the series, that minute respiratory volume studies were not undertaken, and that the evaluation of analgesia and hypnosis is based on clinical impression. However, the high degree of lasting pain relief which resulted in these tense and emotional patients was of an impressive order. Provision of comfort for the patient was the guiding principle and any necessary repeated administrations of the morphine-n-allylnormorphine were not feared. In the cases studied, the administration of this analgesic mixture did not result in either severe or even moderate depression of the maternal respiratory and circulatory systems. Depressed respiratory activity of the newborn was a rare consequence.

Summary

The role of n-allylnormorphine in reversing morphine and other opiate respiratory and circulatory depressant effects is gaining wider acceptance. In order to obtain full advantage of the superior analgesic properties of morphine with minimal side effects, it was decided to mix n-allylnormorphine with each morphine administration. When equal concentrations of 5, 10, or 15 mg. of each of these drugs were mixed and injected into pediatric, geriatric, or obstetric patients, intense sedation and analgesia were produced with either slight or no effect on respiration or circulation. Only slight respiratory depression of one newborn infant resulted in this series from the administration of this analgesic mixture to the mothers in labor. The results obtained with the morphine-n-allylnormorphine mixtures are encouraging and warrant further trial.

Addendum.—Since the completion of this report the morphine-n-allylnormorphine mixture has been administered to an additional 146 obstetric patients in labor. The effect on maternal respiration, pulse rate, blood pressure, and respiration of the newborn has been minimal. In some patients, it appears that the addition of the n-allylnormorphine to the morphine neutralizes to a variable extent its analgesic property. Therefore, we are currently investigating the effectiveness of morphine mixed with lesser concentrations of n-allylnormorphine.

References

1. Wolff, H. G., Hardy, J. D., and Goodell, H.: J. Clin. Investigation **19**: 659, 1940.
2. Unna, K.: J. Pharmacol. & Exper. Therap. **79**: 27, 1943.
3. Hart, E. R., and McCauley, E. L.: J. Pharmacol. & Exper. Therap. **82**: 339, 1944.
4. Smith, C. C., Lehman, E. G., and Gilfillan, J. L.: Federation Proc. **10**: 335, 1951.
5. Huggins, R. A., Glass, W. G., and Bryan, A. R.: Proc. Soc. Exper. Biol. & Med. **75**: 540, 1950.
6. Eckenhoff, J. E., Elder, J. D., and King, B. D.: Am. J. M. Sc. **223**: 191, 1952.
7. Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D.: Anesthesiology **13**: 242, 1952.

A FIVE-YEAR STUDY OF ELDERLY PRIMIPARAS*

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THIS study of 277 elderly primiparas delivered at the Methodist Hospital in Brooklyn, in the years 1943 to 1947, inclusive, is presented to show the major problems of this group of patients and their infants. The "elderly primipara" is here considered to be a woman who is delivered of her first viable child at the age of 35 or over. This group of 277 elderly primiparas occurred in a total of 11,332 births, and they were delivered of 279 infants, two twin pregnancies being numbered in the group.

The past few years have witnessed an increasing number of studies of elderly primiparas. Some of the recent studies are by Dennen and Ainslie[1] at the New York Polyclinic Hospital; Arnot and Nelson,[2] covering a private series in San Francisco; Thompson[3] at the Rotunda Hospital in Dublin, Ireland; Hawkins, Foley, and Tierney[4] at St. Anne's Hospital in Chicago; and Waters and Wager[5] at the Margaret Hague Maternity Hospital in Jersey City. The first table shows a tabulation of some of the findings common to all these studies.

TABLE I. COMPARISON OF SOME STUDIES ON ELDERLY PRIMIPARAS

AUTHORS	PLACE	YEARS	NO. OF PATIENTS	INCIDENCE	CESAREAN SECTION	CESAREAN SECTION RATE	FETAL AND NEONATAL DEATH RATE	MATERNAL DEATHS	MATERNAL MORTALITY/1,000 LIVE BIRTHS
Dennen and Ainslie[1]	New York	1939-48	446	4.2%	168	37.7%	4.4%	1	2.2/1,000 live births
Arnot and Nelson[2]	San Francisco	1922-49	346	3.6%	33	9.5%	8.96%	4	12/1,000 live births
Thompson[3]	Dublin	1944-49	537	2.75%	86	16%	9.7%	1	1.9/1,000 live births
Hawkins, Foley, and Tierney[4]	Chicago	1937-49	383	1.2%	63	16.4%	4.2%	3	8/1,000 live births
Waters and Wager[5]	Jersey City	10 yrs.	649	1.2%	107	16%	6.9%	8	12.3/1,000 live births
Methodist	Brooklyn	1943-47	277	2.46%	47	16.8%	7.5%	1	3.6/1,000 live births

The number of patients ranged from 277 to 649. The incidence of elderly primiparas among total obstetric patients varied from 1.2 per cent to 4.2 per cent and the cesarean section rates ran from 9.5 per cent to 37.7 per cent. It is interesting to note that in four of the studies the cesarean rate was about 16 per cent. The 9.5 per cent section rate of Arnot and Nelson in their series

*Read before the New York Obstetrical Society, March 10, 1953.

of private patients spanned a 28 year period from 1922 through 1949. It is assumed that their cesarean section rate may be weighted by the fact that fewer cesarean sections were performed throughout the country from 1920 to 1940, than after 1940. Gross fetal and neonatal deaths ranged from 4.2 per cent to 9.7 per cent. Although the maternal mortality rates involved totals too small to be valid statistically, they ranged from 2.2 to 12.3 maternal deaths per 1,000 live births.

Incidence in the City of New York and in the Methodist Hospital

A comparison of percentages of elderly primiparas delivered in the City of New York with those delivered in the Methodist Hospital is given in Tables II and III and reveals a rather marked similarity of the two groups. Since the hospital incidence corresponds closely to that of the city, the hospital experience in regard to the number of these patients and their problems may be considered typical for the City of New York.

TABLE II. BIRTHS REPORTED AND ELDERLY PRIMIPARAS IN THE CITY OF NEW YORK, 1943-1947

	1943	1944	1945	1946	1947	TOTAL
Total births	134,520	122,748	128,853	152,736	171,174	710,031
Total first child	57,503	48,311	48,321	64,374	75,966	294,475
Total first child of mother aged 35 or more	2,703	2,769	2,885	3,356	3,800	15,513
Percentage of first child of elderly primipara/total births	2.00%	2.25%	2.24%	2.20%	2.22%	2.18%

TABLE III. INCIDENCE OF ELDERLY PRIMIPARAS

	1943	1944	1945	1946	1947	TOTAL
City of New York.— Percentage of first child of elderly primipara/total births	2.00%	2.25%	2.24%	2.20%	2.22%	2.18%
Methodist Hospital.— Percentage of first child of elderly primipara/total births	2.21%	2.95%	2.59%	2.48%	2.16%	2.46%

Private and Ward Services

In Table IV the distribution of these patients with regard to private and ward services is noted. Ninety-four per cent of the elderly primiparas were delivered on the private service, though only 71 per cent of the total patients were in private accommodations. This indicates that a much larger percentage of elderly primiparas was given private care. It is thought that this is due to the greater financial stability of, and the greater desire for individual care by, the older patients having their first obstetric experience.

Sex of Infants

Of the 279 infants, 134 were male and 145 were female.

TABLE IV. DISTRIBUTION OF PRIVATE AND CLINIC PATIENTS, METHODIST HOSPITAL, YEARS 1943-1947

	1943	1944	1945	1946	1947	TOTAL
Private service	41	57	50	56	56	260 (94%)
Ward service	7	3	4	2	1	17 (6%)
Total patients	48	60	54	58	57	277 (100%)

Annual and Total Statistics

Analysis of the statistics for the elderly primiparas as compared with the total number of deliveries in the hospital points out several significant facts. Since there were 279 infants delivered of these 277 patients, we will consider the fetal statistics on the basis of the babies delivered. It will be seen from Tables VI and VII that the older patients were much more frequently subjected to cesarean section, 16.82 per cent as opposed to 3.90 per cent for all patients. This cesarean section rate is lower than the 37.7 per cent reported by Dennen, and higher than the 9.5 per cent of Arnot's series, but it is practically the same as that reported in the studies at Dublin, Chicago, and Jersey

TABLE V. ANNUAL STATISTICS FOR ALL PATIENTS AND ELDERLY PRIMIPARAS, METHODIST HOSPITAL, YEARS 1943-1947

	1943	1944	1945	1946	1947	TOTAL
All Patients.—						
Total births	2,167	2,066	2,086	2,337	2,676	11,332
Total cesarean sections	69	87	89	92	105	442
Percentage of cesarean sections	3.2%	4.2%	4.3%	3.9%	3.9%	3.90%
Maternal deaths	2	3	4	3	3	15
Maternal mortality (per 1,000 live births)	0.92	1.46	1.92	1.28	1.12	1.32
Premature infants (5½ pounds or less)	118	112	113	144	127	614
Percentage of premature infants	5.44%	5.42%	5.42%	6.20%	4.75%	5.41%
Neonatal deaths	32	38	35	32	45	182 (1.6%)
Stillbirths						
Viable	37	45	42	25	32	181 (1.6%)
Nonviable	56	48	32	35	35	206 (1.8%)
Total stillbirths	93	93	74	60	67	387 (3.4%)
Elderly Primiparas (Aged 35 or More at Time of Delivery).—						
Total births	48	61	54	58	58	279
Total cesarean sections	5	11	10	10	11	47
Percentage of cesarean sections	10.4%	18.0%	18.5%	17.2%	18.9%	16.82%
Maternal deaths	1	0	0	0	0	1
Maternal mortality (per 1,000 live births)	20.8	0	0	0	0	3.58
Premature infants	4	6	3	5	5	23
Percentage of premature infants	8.3%	9.8%	5.5%	8.6%	8.6%	8.24%
Neonatal deaths	2	1	1	5*	0	9 (3.2%)
Stillbirths						
Viable	2	2	5	1	1	11 (3.9%)
Nonviable	0	1	0	0	0	1 (0.36%)
Total stillbirths	2	3	5	1	1	12 (4.3%)
Percentage of first child of elderly primipara/total births	2.21%	2.95%	2.59%	2.48%	2.16%	2.46%

*Includes one death on the fifty-fourth day of acute upper respiratory infection.

City. The maternal mortality rate for all patients was 1.32 per 1,000 live births and for the elderly primiparas 3.58 per 1,000 live births. This latter figure for maternal mortality is not statistically valid, dealing as it does with such a small number of cases, but it is being included to complete the table.

TABLE VI. SUMMARY OF STATISTICS, METHODIST HOSPITAL, YEARS 1943-1947

	TOTAL	ELDERLY PRIMIPARA
Births	11,332	279
Cesarean sections	442	47
Percentage of cesarean sections	3.90%	16.82%
Maternal deaths	15	1
Maternal mortality per 1,000 live births	1.32	3.58
Premature infants (5½ pounds or less)	614	23
Percentage of premature infants	5.41%	8.24%
Stillbirths		
Viable	181 (1.6%)	11 (3.9%)
Nonviable	206 (1.8%)	1 (0.36%)
Total stillbirths	387 (3.4%)	12 (4.3%)
Neonatal deaths	182 (1.6%)	9* (3.2%)

*Includes one death on the fifty-fourth day.

Maternal Deaths

Abstract of the one maternal death follows:

Patient H. B., chart No. 28955, was admitted via ambulance on Dec. 18, 1943, with the diagnosis of lobar pneumonia and active labor. The patient was delivered by means of low forceps and a right mediolateral episiotomy, 2½ hours after admission, of a 6 pound, 10½ ounce baby girl, in good condition at the time of birth. Total labor was 25 hours and 45 minutes. The infant died 3 hours and 12 minutes after birth. The mother died at 3:07 P.M. on Dec. 19, 1943, 20 hours and 29 minutes after delivery. Hemolytic pneumococci were identified in the mother's sputum. No autopsy was obtained. The diagnosis was: lobar pneumonia, pregnancy delivered, neonatal death, maternal death.

Prematurity, Stillbirths, and Neonatal Deaths

Prematurity was a more frequent complication of the child of the elderly primipara, exhibiting itself in 8.24 per cent as against 5.41 per cent for the total number of deliveries. Stillbirths were one-fourth again as frequent in the older patients and neonatal deaths were twice as frequent, so that in this group of older mothers the chance of fetal survival was markedly reduced.

The causes of death among the stillbirths were: premature separation of the placenta in 2 cases; intrauterine asphyxia in 2 cases; 1 case each for fibrotic placenta, subarachnoid hemorrhage plus phlebitis of the umbilical cord, and multiple infarcts of the placenta; and 4 cases of unknown etiology. There were 3 necropsies of these 11 stillborn infants. The causes of the 9 neonatal deaths were: premaurity in 5 cases, and 1 case each for bronchopneumonia, hemorrhage in both adrenals, upper respiratory infection, and acute maternal infection. One death from acute respiratory infection (Case 5) occurred on the fifty-fourth day of life and is not actually a neonatal death, but has been included to simplify the tabulation. There were 2 necropsies of these 9 cases.

TABLE VII. ABSTRACTS OF VIABLE STILLBORN INFANTS

CHART NO.	DATE	DELIVERY	WEIGHT	SEX	WEEKS	REMARKS
1. 26547-A	3/18/43	Low forceps Right mediolateral episiotomy	8 pounds, 3¼ ounces	M	39	Macerated stillborn infant. Premature separation of placenta. Labor 4 hours, 15 minutes. Vertex right occipitotransverse. No autopsy.
2. 28558	9/ 7/43	Craniotomy	3 pounds	F	32	Macerated stillborn infant. Labor 3 hours, 10 minutes. Breech. Pathology report: Fibrotic placenta. No autopsy.
3. 29479	5/ 4/44	Low forceps Right mediolateral episiotomy	7 pounds, 12¼ ounces	M	40	Fetal heart irregular and slow at 8:45 A.M. Stillborn infant delivered at 8:55 A.M. Vertex right occipitoanterior. Labor 15 hours, 2 minutes. Autopsy: Subarachnoid hemorrhage and phlebitis of umbilical vein.
4. 30196	10/23/44	Breech extraction Piper forceps Right mediolateral episiotomy	6 pounds, 12 ounces	M	40	Difficult delivery, extended arms. Frank breech. Labor 20 hours. Ruptured membranes 52 hours, 50 minutes. Intrauterine asphyxia. No autopsy.
5. 30636	2/ 7/45	Low forceps Right mediolateral episiotomy	8 pounds, 5 ounces	F	40	Macerated stillborn infant. Fetal heartbeat lost during first stage of labor. Labor 9 hours, 42 minutes. Vertex right occipitoanterior. Autopsy: Asphyxia, thrombosis of umbilical vein.
6. 30872	4/ 1/45	Low forceps Right mediolateral episiotomy	5 pounds, 6¼ ounces	M	40	No activity noted by mother since 3/30/45. No fetal heartbeat on admission. Labor 9 hours, 5 minutes. Vertex right occipitoanterior. Autopsy: Cause of death not known.
7. 31140	6/21/45	Spontaneous	5 pounds, 2¾ ounces	M	35	Patient admitted on account of vaginal bleeding and cramps. No fetal heartbeat on admission. Labor 1 hour, 19 minutes. Vertex left occipitoanterior. Macerated stillborn infant. Premature separation of placenta. No autopsy.
8. 31699	11/24/45	Craniotomy	4 pounds, 3 ounces	M	45	No fetal heartbeat 2 days prior to admission. Induction by rupture of membranes and bag. Labor 2 hours, 41 minutes. Vertex left occipitoanterior. Macerated stillborn infant. No autopsy.
9. 31441	9/21/45	Low classical section	10 pounds, 4¼ ounces	M	40	Elective section. Membranes ruptured 4 days. Vertex right occipitoanterior. Macerated stillborn infant. No autopsy.
10. 32017	2/26/46	Low classical section	5 pounds, 3¼ ounces	M	38	Macerated stillborn infant. Mother decompensated twice in pregnancy. Hypertensive cardiac disease with aortic stenosis. Elective section and tubal ligation. Vertex left occipitoanterior. No autopsy.
11. 33887	4/11/47	Spontaneous	4 pounds	F	35	Mild pre-eclampsia. Stillborn infant. Labor 3 hours, 46 minutes. Vertex right occipitoanterior. Multiple infarcts of placenta. No autopsy.

TABLE VIII. ABSTRACTS OF NEONATAL DEATHS

CHART NO.	DATE	DELIVERY	WEIGHT	SEX	WEEKS	REMARKS
1. 22907-B	5/17/43	Breech extraction	12 ounces	F	27	Spontaneous rupture of membranes. Labor 9 hours, 40 minutes. Double footling breech. Baby died 40 minutes after birth. No autopsy.
2. 28955	12/18/43	Low forceps Right mediolateral episiotomy	6 pounds, 10½ ounces	F	40	Mother had lobar pneumonia. Delivered 2½ hours after admission. Total labor 25 hours, 45 minutes. Vertex right occipitoanterior. Died 3 hours, 12 minutes after birth. No autopsy. Maternal death.
3. 29994	9/ 9/44	Low forceps Right mediolateral episiotomy	4 pounds, 10 ounces	F	40	First of twins delivered. Labor 2 hours, 3 minutes. Vertex left occipitoanterior. Infant died 10/5/44, 27 days, hypostatic pneumonia. No autopsy.
4. 81414	8/30/45	Assisted breech	2 pounds	M	25	Premature labor. Labor 8 hours, 49 minutes. Double footling. Infant died 3 hours, 10 minutes. No autopsy.
5. 32028	2/28/46	Low forceps Left mediolateral episiotomy	2 pounds, 11¼ ounces	M	29	Premature separation of placenta. Labor 5 hours, 30 minutes. Vertex left occipitoanterior. Died fifty-fourth day at weight 4 pounds, 15 ounces, of acute upper respiratory infection. Autopsy.
6. 32067	3/10/46	Spontaneous Median episiotomy	4 pounds, 14½ ounces	F	32	Polyhydramnios. Labor 8 hours, 37 minutes. Vertex left occipitoanterior. Mongolian idiot. Died 4/4/46 of bronchopneumonia.
7. 33181	11/26/46	Low forceps Right mediolateral episiotomy	9 pounds, 3 ounces	F	40	Labor 11 hours. Baby markedly asphyxiated. Resuscitated with difficulty. Died after 44 hours. Autopsy: hemorrhage of both adrenals.
8. 33246	12/ 9/46	Spontaneous Right mediolateral episiotomy	2 pounds, 11½ ounces	M	28	Premature rupture of membranes. Labor 10 hours, 12 minutes. Vertex right occipitoanterior. Died at 24 hours. No autopsy.
9. 33302	12/20/46	Spontaneous	2 pounds, 1 ounce	F	28	Spontaneous delivery at home. Died 20 minutes after admission. No autopsy.

Congenital Anomalies

Congenital anomalies were present in 11 of the 279 infants. This included 3 cases of Mongolism, an incidence of 1.08 per cent. Among the 11,053 other births for these years, there were 15 cases of Mongolism, an incidence of 0.14 per cent. Thus Mongolism was about eight times more frequent in the children of elderly primiparas than it was among other infants born in the hospital, which is in agreement with statements in Benda's[6] *Mongolism and Cretinism* and in the article by Böök and Reed[7] titled "Empiric Risk Figures in Mongolism."

TABLE IX. INFANT ANOMALIES

Congenital.—		
Mongolism	3	
Clubfoot	2	
Clubfeet	2	
Cleft palate and naris	1	
Spina bifida and myelomeningocele	1	
Hypospadias	1	
Absent ear	1	
Congenital total	11	
Acquired.—		
Fractured clavicle	1	
Transient facial and Erb's palsies	1	
Acquired total	2	
Mongolism	3	(1.08%)
Mongolism in 11,053 births excluding 279 infants of elderly primiparas	15	(0.14%)

TABLE X. TYPE OF LABOR

TYPE OF LABOR	1943	1944	1945	1946	1947	TOTAL
Rapid (under 6 hours)	9	10	6	12	9	46
Normal (6 to 20 hours)	28	37	31	35	30	161
Prolonged (over 20 hours)	9	8	13	8	12	50
No labor (elective sections)	2	5	4	3	6	20
Total patients	48	60	54	58	57	277

Type of Labor

Labor has been classified as rapid if under six hours, normal if between six and twenty hours, and prolonged if over twenty hours. By these criteria, 46 patients had rapid labors, 161 had normal labors, and 50 had prolonged labors. Dennen reported 248 (89 per cent) out of 278 elderly primiparas who had vaginal deliveries had labors of less than 24 hours, Hawkins reported 260 (78 per cent) out of 330 such patients had labors of less than 24 hours, and we found 194 (84 per cent) out of 232 such patients had labors of less than 20 hours. Twenty patients, who had elective cesarean sections, had no labor. The longest labor was 79 hours, and, after this trial, the patient had a cesarean section, the primary indication being uterine inertia.

Presentation and Position

There were 257 vertex presentations accounting for 92.1 per cent of all cases, 20 breech presentations for an incidence of 7.2 per cent, and 2 other presentations amounting to 0.7 per cent. One of the 20 breech presentations was one of twins, giving a corrected total of 19, or 6.8 per cent. Thompson

reported a 6.6 per cent incidence of breech presentations in the Rotunda Hospital study. The 25 year average at the Methodist Hospital for primiparous breech presentations excluding multiple pregnancies is 4.6 per cent.[8] The incidence of breech presentations in elderly primiparas was half again as high as the hospital average for all primiparas.

TABLE XI. PRESENTATION AND POSITION

Vertex.—		
Left occipitoanterior	131	
Left occipitotransverse	8	
Left occipitoposterior	25	
Right occipitoanterior	62	
Right occipitotransverse	6	
Right occipitoposterior	24	
Occipitoposterior	1	
Total	257	(92.1%)
Breech.—		
Right sacroanterior	9	
Left sacroanterior	10	
Unspecified	1	
Total	20	(7.2%)
Face, right mentoposterior	1	
Not stated	1	
Total births	279	(100%)

Method of Delivery

There was a total of 232 vaginal deliveries and 47 cesarean sections. The vaginal deliveries included 21 normal spontaneous births of which one was a breech. Of the forceps deliveries, 166 were low, 33 were mid, 1 application was to a frank breech, and 4 were for the aftercoming head. There were no high forceps applications. Breech presentations were delivered as assisted breech in 3 cases and breech extraction in 6 cases. Two craniotomies were employed on stillborn fetuses. One was a breech presentation of a macerated stillborn infant that weighed three pounds. The second was performed in the case of a patient in whom no fetal heartbeat had been heard for two days prior to hospital admission in the forty-fifth week of gestation by dates. Labor was induced by rupture of the membranes and bag insertion. The macerated stillborn infant weighed 4 pounds, 3 ounces.

TABLE XII. METHOD OF DELIVERY

METHOD OF DELIVERY	1943	1944	1945	1946	1947	TOTAL
Vaginal.—						
Normal spontaneous	4	6	4	5	2	21
Operative						
Low forceps	27	35	30	39	35	166
Midforceps	9	5	8	4	7	33
High forceps	0	0	0	0	0	0
Forceps to breech	0	1*	0	0	0	1
Assisted breech	1	0	1	0	1	3
Breech extraction	1	3*	0	0	2*	6
Craniotomy	1	0	1	0	0	2
Total vaginal	43	50	44	48	47	232
Abdominal, total	5	11	10	10	11	47
Total births	48	61	54	58	58	279
*Forceps for aftercoming head	0	3	0	0	1	4

TABLE XIII. MODE OF DELIVERY OF BREECH PRESENTATIONS

Breech extraction	6*
Assisted breech	3
Spontaneous breech	1
Cesarean section	8
Craniotomy	1
Forceps application to breech	1
Total	20

*Includes one of twins.

Cesarean Sections

There were 47 cesarean sections, of which 20 were elective and 27 were performed after a trial of labor (Table XIV).

The primary indications for the 20 elective sections are indicated in Table XV. "Elderly primigravida" was given as a secondary indication in 6 of the 7 cases of cephalopelvic disproportion. While "elderly primigravida" was not written as a secondary indication in the 6 breech presentations, it was

TABLE XIV. TYPES OF CESAREAN SECTIONS AND PRESENTATION IN SECTIONS

Type of Cesarean Section.—	
Low flap	20
Low classical	21
Classical	3
Extraperitoneal	3
Total sections	47
Elective	20
After trial of labor	27
Presentation in Sections.—	
Vertex	39
Total vertex presentations	259
Percentage of vertex presentations sectioned	15.1%
Breech	8
Total breech presentations	19*
Percentage of breech presentations sectioned	42.1%

*Excluding breech of twins.

TABLE XV. INDICATIONS FOR CESAREAN SECTIONS

Elective.—	
Cephalopelvic disproportion	7
Breech presentation	6
Elderly primigravida	2
Pre-eclampsia, severe	1
Marginal placenta previa	1
Ruptured membranes	1
Cul-de-sac fibroid	1
Cardiac decompensation	1
Total elective sections	20
After Trial of Labor.—	
Cephalopelvic disproportion	10
Uterine inertia	8
Elderly primigravida	3
Breech presentation	2
Pre-eclampsia, severe	1
Occult prolapse of umbilical cord	1
Previous trachelorrhaphy	1
Multiple fibroids	1
Total after trial of labor	27
Total cesarean sections	47

tacitly implied in the charts. Thus 14 of the 20 elective sections were performed primarily or secondarily because the patients were elderly primigravidas.

The primary indications for the 27 cesarean sections after a trial of labor also are indicated in Table XV. The secondary indication of "elderly primigravida" was written or implied in the cases of cephalopelvic disproportion, uterine intertia, and breech presentation. Thus 23 of 27 cesarean sections after a trial of labor were performed primarily or secondarily because the patients were elderly primigravidas.

Concern for the safety of the infant appears to have more weight in the consideration of cesarean section in the case of the elderly primigravida than in the young primigravida, because of the fewer years of reproductive potential remaining for these patients. All the living babies delivered by cesarean section in this group of patients were discharged from the hospital in good condition.

Morbidity

The most frequent cause of morbidity is the category designated "unknown." In reviewing the charts, the term "postoperative reaction" was given as the cause of morbidity in several of the cesarean sections, but in the absence of definite findings in the laboratory reports and the physical examinations, we have listed such cases in the "unknown" category.

TABLE XVI. MATERNAL MORBIDITY AND CAUSES

Maternal Morbidity, 100.4° F. Scale.—	
None	251
One day	1
Two days	11
More than two days	14
Total mothers	277
Causes of Morbidity.—	
Unknown	13
Cystitis-pyelitis	4
Endometritis	3
Mastitis	2
Bronchitis	1
Wound infection	1
Sponge in vagina	1
Parametritis	1
Total	26

Antepartum Complications

There were 13 cases of toxemia among the elderly primiparas for an incidence of 4.7 per cent as compared with 270 cases for all obstetric patients for the years under study, or 2.2 per cent. Dennen reported 4.3 per cent cases of toxemia, Arnot 6.8 per cent, and Waters 11.9 per cent among their elderly primiparas. Both Arnot and Waters indicate that the incidence of toxemia is significantly higher among elderly than among young primiparas, which is in agreement with our findings. There were no cases of eclampsia among our elderly primiparas, although there were 10 cases of eclampsia among the other obstetric patients for this period.

TABLE XVII. ANTEPARTUM COMPLICATIONS

Placenta previa	0
Low implantation of placenta	1
Premature separation of placenta	4
Total cases of hemorrhage	5
Pre-eclampsia, mild	10
Pre-eclampsia, severe	3
Eclampsia	0
Total	18

Postpartum Complications

There were 16 cases of postpartum complications among our 277 patients, including 5 cases of hemorrhage, 4 cases of cystitis and/or pyelitis, and 2 cases of phlebitis.

TABLE XVIII. POSTPARTUM COMPLICATIONS

Hemorrhage	5
Cystitis-pyelitis	4
Phlebitis	2
Retained secundines	1
Parametritis	1
Wound infection	1
Coccydynia	1
Acute mastitis	1
Total	16

Previous Abortions

Forty-two, or 15 per cent, of the 277 elderly primiparas had histories of one or more previous abortions. One patient had 5 previous abortions during a previous marriage. Another patient had 6 previous abortions before being able to carry a pregnancy to a successful termination.

TABLE XIX. PREVIOUS ABORTIONS

One abortion	30
Two abortions	9
Three abortions	0
Four abortions	1
Five abortions	1*
Six abortions	1
Total previous abortions	42 (15%)
No abortions	235 (85%)
Total patients	277 (100%)

*This patient had five spontaneous abortions during a previous marriage.

Summary

A study of 277 elderly primiparas delivered at the Methodist Hospital of Brooklyn in the years 1943 to 1947, inclusive, has been presented. A comparison has been made of our findings with those reported in recent similar studies. Our incidence of these patients, 2.46 per cent, was higher than the 1.2 per cent reported by Hawkins and by Waters, and lower than the 2.75 per cent reported by Thompson, the 3.6 per cent reported by Arnot, and the 4.2 per cent reported by Dennen. Our cesarean section rate was practically the same as that reported by Thompson, Hawkins, and Waters, higher than that reported by Arnot, and less than half that reported by Dennen.

The similarity in the incidence of elderly primiparas in the City of New York and at the Methodist Hospital has been demonstrated, so that the hospital experience in regard to the number of these patients and their problems may be considered as typical for the city as a whole.

As compared with other hospital obstetric patients, elderly primiparas more often seek private care, and they have a cesarean section rate over four times as great, a premature rate half again as great, double the neonatal mortality rate, eight times the incidence of Mongolism, and twice the incidence of toxemia.

Acknowledgment and thanks are given to Dr. Henry S. Acken, Jr., for his advice and assistance in organizing this material, and to Mr. Herbert Rich, Senior Statistician of the Bureau of Records and Statistics of the Department of Health of the City of New York, for supplying the pertinent city birth statistics.

References

1. Dennen, E. H., and Ainslie, W. H.: Postgrad. Med. **10**: 241, 1951.
2. Arnot, P. H., and Nelson, D. R.: West. J. Surg. **58**: 535, 1950.
3. Thompson, E. W. L.: Practitioner **166**: 133, 1951.
4. Hawkins, R. J., Foley, W. E., Jr., and Tierney, T. M.: West. J. Surg. **59**: 13, 1951.
5. Waters, E. G., and Wager, H. P.: Am. J. Obst. & Gynec. **59**: 296, 1950.
6. Benda, C. E.: Mongolism and Cretinism, ed. 2, New York, 1949, Grune & Stratton, p. 281.
7. Böök, J. A., and Reed, S. C.: J. A. M. A. **143**: 730, 1950.
8. Beil, A. R.: Personal communication.

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Discussion

DR. DONALD G. JOHNSON.—I should like to mention briefly the experiences of the New York Lying-In Hospital since 1932. We have reviewed two separate series of elderly primiparas, a total of some 1,824 patients which gives an approximate incidence of about 3 per cent of our total population. Our cesarean section rate in the 1,824 patients was approximately 23 per cent. There was a definite increase in the second series studied, the first ending in 1944, the second in 1950. At the completion of the first series it was our feeling that the fetal mortality rate of approximately 8 per cent was much too high and that a greater liberalization of the indications for cesarean section should be considered. In consequence of that observation a change in policy was introduced concerning the treatment of breech presentations in elderly primigravidas, for example, and more frequent management by cesarean section was recommended. There were other factors which perhaps played a role in the reduction of fetal mortality from approximately 8 per cent to 3½ per cent with the completion of the second series but we felt an increase in cesarean sections from 13 per cent to 23 per cent in the second series accounted for some degree of improvement in our fetal end results.

DR. HENRY S. ACKEN, JR.—Cesarean section is a factor to be seriously considered in the elderly primipara. Since she is of an age when pregnancy is not likely to occur frequently, unnecessary risk in delivery is not justifiable. Dr. Johnson's figures bear out that fact also.

Breech presentation in the elderly primipara is perhaps especially deserving of cesarean section. The fact that fetal abnormalities may occur in the elderly primipara should not, I believe, deter us from using cesarean section as a method of delivery.

DR. GEORGE W. KOSMAK.—It would be interesting to know something about the fertility of these patients. How long had these women been married before they had their pregnancies and was anything done to relieve the sterility in that particular group? I think it would be interesting to take that into account. Why were there so many elderly primiparas?

DR. A. CHARLES POSNER.—In the analysis of our work at the Harlem Hospital we reported 139 cases during the period of 1939 to 1943. The incidence of elderly primiparas

was 0.4 per cent. We had a cesarean rate of 25 per cent, a toxemia rate of about 25 per cent, a fibroid rate of about 6 per cent, and premature rupture of membranes of 8.6 per cent.

One thing not mentioned here that seems interesting is the male-female sex ratio in infants of elderly primiparas. In our experience the ratio of males to females was 124 to 100.

DR. EDWARD H. DENNEN.—I enjoyed Dr. Weisl's detailed report of the elderly primiparas and felt highly complimented at his liberal reference to our article. I must say that I think our study is not an average sample. It is more of a selected sample as shown by the high incidence of elderly primiparas, over 4.0 per cent, and also because of the fact that at our hospital the incidence of private patients to ward patients is more than three to one, and a very large proportion of them are referred complicated cases.

That brings up the point of the high incidence of cesarean section. That incidence rose as time progressed in our study of some 450 elderly primiparas, covering the period of ten years. Within the first five-year period the incidence of cesarean was about 30 per cent. The gross over-all infant fetal and infant mortality was over 7 per cent. In the second five-year period the incidence of cesarean was raised to 40 per cent, and the infant mortality, uncorrected, stillbirth and neonatal, dropped to 2.8 per cent. Another feature in the increased incidence was the thought of the possible morbidity, of the troubles that might occur following the delivery from below. Incidentally, the incidence of forceps delivery and spontaneous births did not change very much in the two five-year periods. The change was in the cesarean rate. We did not have an over-all check of the morbidity, but we found that we avoided the difficulties that came in certain cases of elderly primiparas, the particular trouble of cystocele, with more frequent use of cesarean.

A typical example is one which seems like a favorable case at the onset of labor, with the head engaged and the cervix such as to make one feel that there would be a short first stage and that the labor would continue that way. In a very short time the cervix is three-fourths dilated but from then on the progress is little, if any, and with the head well down in the pelvis and so much dilatation one hates to change his mind as to the method of procedure, and, continuing, has considerable difficulty in getting the case to full dilatation. Following that, there is a difficult forceps delivery. It has been our experience that a certain number of these cases have trauma to the vagina, particularly cystocele.

DR. WEISL (Closing).—Dr. Johnson at the New York Lying-In had a much larger group of patients than we had to work with but I think what he reported was more or less in agreement with the trend today. I believe that was brought out in reviewing the one report of a private series that was mentioned, Arnot and Nelson of San Francisco, with a study covering the years from 1922 to 1949, with a section rate of 9.5 per cent. I did not break those figures down, but I think it is a fair assumption that from 1920 to 1940 the mortality from cesarean section was a formidable risk to take. In studies done since then and in all hospitals, there has been an increase in the incidence of abdominal delivery in preference to a difficult midforceps or difficult vaginal delivery.

The question of fertility that Dr. Kosmak brought up is interesting. Many of these patients had fertility problems, but some of them were patients who married late, and we had the period of the war in there, too, from 1943 to 1947, so that some women who might have been married in the thirties might not have had a chance to conceive. I do have a breakdown on the number of abortions. Of these 277 patients, 42, that is 15 per cent, had previous abortions, 85 per cent had no previous abortions. The number of abortions ranged from one to six. Most of them, 30 patients, had one abortion; 9 had two; none had three; one had four; one had five; and one had six. The patient who had five abortions had them during a previous marriage and when she remarried she carried her sixth pregnancy to term. The one patient with six abortions was under the care of one of our obstetricians and finally achieved a living child.

As for the sex ratio that Dr. Posner asked about, we did not find anything startling. Of the 279 infants, 134 were male and 145 were female.

THE USE OF HORMONES FOR THE PREVENTION OF BREAST ENGORGEMENT AND LACTATION

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MANY papers have been written concerning the use of various hormones in the puerperium to prevent engorgement of the breast and lactation. However, there has been considerable disagreement concerning the efficacy of these substances and the optimal dosages necessary to control this function during this period. It has also been a debatable problem as to the best time to start this medication. With these uncertainties in mind, a study was undertaken to evaluate the effects of two hormonal substances on the control of the secretion of the breast in the puerperium.

The first material used was an estrogen-androgen combination designated as Estan.* This was given orally. The second material employed was testosterone propionate given intramuscularly.

Selection of Patients

The patients chosen for this study were both primigravidas and multigravidas. It was possible to use these individuals for this study because some had designated that they did not care to nurse their babies, while others were not permitted to nurse for a variety of reasons. Among the multigravidas who did not desire to nurse, the following reasons were the most prominent: (1) insufficient quantities of milk, (2) mastitis, and (3) fissured or bleeding nipples. All objections were based upon previous experiences.

The main reason in the primigravid group was generally economic. These individuals found it necessary to return to work as soon as convalescence permitted. Nursing was not started in these patients. Other individuals in both groups were not permitted to nurse because of the following complications: (1) toxemia of pregnancy, (2) Rh iso-immunization, and (3) prematurity.

The Physiology of Lactation

Although mammary growth occurs during pregnancy, the flow of milk is not established until after the birth of the fetus and the expulsion of the placenta. Complete information concerning the factors which initiate milk secretion after the birth of the fetus is not available.[1] However, most authorities consider that there are two factors in this process, namely, hormonal and nervous. Since this paper deals with hormones, the discussion will limit itself to this factor only.

*Estan, 5 mg. methyltestosterone and 0.25 mg. dienestrol. Supplied by the White Laboratories, Kenilworth, N. J.

As a result of a number of observations, the hormonal release theory of mammary secretion was proposed. Secretion of milk by the breast is dependent upon the stimulus of the lactogenic hormone (prolactin) produced by the anterior pituitary. This hormone is most effective when the breast has been previously subjected to estrogen and progesterone stimulation.[2] Turner and his associates[3, 4] indicate that estrogen alone is actually capable of increasing the lactogenic hormonal content of the pituitary which effect may be offset by pregnancy. During pregnancy, it therefore appears that two factors operate to prevent lactation: (1) the growth stimulus of estrogen on the breast, and (2) the inhibition of lactogenic hormone production by progesterone.[5] With the decrease in the amount of estrogen and progesterone accompanying parturition, the physiological conditions become more favorable for the lactation process to take place. This theory does not explain the postpartum increased production of lactogenic hormone. Selye and co-workers[6] have concluded that nursing promotes milk secretion by reflex stimulation of the hypophysis to secrete its lactogenic hormone.

Concept of Action

Ribson[7] was the first to demonstrate that testosterone was effective in the suppression of lactation. He did this experimentally in mice, employing 0.1 mg. of the substance for 20 days. Kurzrok and O'Connell[8] reported success in preventing lactation in 19 out of 21 patients, employing 50 to 150 mg. of testosterone. These two investigators further stated that a single dose of 150 mg. was not as effective as 25 mg. employed twice daily or 50 mg. daily for three days.

Testosterone has been shown to suppress the pituitary gland and as a consequence also to limit ovarian function.[9] In addition, since it suppresses the pituitary, it no doubt inhibits the production of the lactogenic hormone which is responsible for making the breast secrete.[10] This inhibitory substance has been shown to be free of undesirable side effects provided that the dosage does not exceed 300 mg. per month.[9] Some investigators state that the dosage should not exceed 200 mg. per month. In all events, the amount of testosterone propionate employed in this study did not approximate either of the aforementioned dosages.

Estrogens,[12, 13] particularly diethylstilbestrol, as well as alpha estradiol, estrone, and dienestrol, have been found to be effective in the prevention of engorgement and lactation. However, Stewart and Pratt[12] have emphasized the fact that engorgement and lactation are not synonymous and that, further, the inhibition of one does not mean that the inhibition of the other necessarily follows.

The mechanism by which estrogens prevent or relieve engorgement and depress lactation remains unsolved. Two explanations that appear possible have been offered:

1. They depress the pituitary and in so doing depress the production or the release of the lactogenic hormone (prolactin).

2. Estrogens, through their stimulating action on breast tissue, interfere with the response of the areolae to the lactogenic hormone.[14]

In spite of the good immediate results obtained with estrogens, they fell into disrepute and disregard due to nausea, vomiting, withdrawal bleeding, and the return of both lactation and engorgement. Because of these undesirable effects, a combination of estrogens and androgens began to be employed by many investigators.

Greenblatt and associates[15] in their study of estrogen-androgen combinations came to the conclusions that these substances together modify the specific action of each other but do not neutralize one another. In other words, they have a synergistic action. Salter[9] states that the neutralization of the female hormone, estrogen, by androgen may be proved by applying locally a mixture of these substances in equal amounts. One can readily see, therefore, that there is still disagreement in regard to this matter and until more investigative work is done to substantiate one or the other claim, one must accept the fact that we really do not know how these substances work when utilized in conjunction with one another. With this in mind, it is the purpose of this paper to add our experiences with these substances to the literature.

Materials and Methods

There were 176 patients in whom an attempt was made to inhibit the process of lactation. These individuals were divided into three groups. All patients were observed by the resident and nursing staffs. These patients were allowed to eat and drink as they desired and no method of compression was attempted. Brassieres or light breast binders were allowed for purposes of support.

The first group consisted of 36 patients who received 50 mg. of testosterone propionate intramuscularly for 3 days beginning the day after delivery. Of this number, 34 were multigravidas and 2 were primigravidas.

The second group was given Estan, an oral combination of estrogen and androgen, 1 tablet three times a day for 5 days starting the first 24 hours post partum. There was a total of 48 patients in this group, 36 being multigravidas and 12 primigravidas.

The third group of patients received Estan also. However, the dosage was increased to 2 tablets three times a day for 5 days beginning the day after delivery. There were 92 patients in this group, 66 of whom were multigravidas and 26 primigravidas.

Results

In the testosterone group, lactation did not occur in any of the patients. Engorgement and pain appeared on the third day and became worse on the fourth day, gradually subsiding before the patient was discharged from the hospital. The symptoms were severe enough that the patients complained of them and the engorgement was confirmed by examination.

The second group of patients, who received 1 tablet of Estan three times a day for 5 days, was composed of 19 individuals without any symptoms and 7 who complained of tenderness only. Therefore, the results in these 26 individuals were thought to be good, thereby making a total of 55 per cent in whom the treatment was considered satisfactory.

In the testosterone group as well as both groups with Estan, there was no lactation present. The tenderness, pain, and engorgement appeared on the third, fourth, and fifth postpartum days with the Estan, but not to the same extent that it did in the testosterone group. However, since the patients complained of these symptoms, the results in the second group were considered poor in 45 per cent of the cases.

The third group of patients who received 2 tablets of Estan three times a day for 5 days was made up of 45 individuals without any symptoms. Tenderness was present only to a minimal degree in 30 patients and, therefore, the results were considered good in this number. Once again in 17 patients engorgement, pain, and tenderness appeared on the third, fourth, or fifth postpartum day and, as a consequence, the results were thought to be poor in 18.4 per cent of the cases in this group. The total number of patients who obtained excellent to good results was 75, 81.6 per cent.

Comment

In the past, various types of medication have been employed to depress lactation and prevent engorgement in the puerperium with little or no success. The estrogenic substances were disregarded because of their undesirable side effects, such as nausea, vomiting, and withdrawal bleeding, and other substances were employed such as testosterone and progesterone, but they did not appear to be completely satisfactory.

We have attempted to evaluate the use of an oral estrogen-androgen combination, Estan, in the prevention of lactation and engorgement. In our study, no undesirable side effects were encountered either in the hospital or at home. Particularly significant was the fact that there was no withdrawal bleeding present in these patients.

The nursing personnel in our Obstetrical Department stated that Estan was the best medication that had been used in the Department in recent years, in comparison to estrogens or testosterone alone. In addition, patients who heard of the medication from their friends asked for it in the hospital, stating that they had diethylstilbestrol or testosterone the last time and it didn't work. This latter group of patients experienced complete satisfaction with Estan.

Summary

Lactation was inhibited completely by employing an estrogen-androgen combination, Estan, for 5 days orally, 1 and 2 tablets three times a day, or testosterone propionate alone parenterally, 50 mg. daily for 3 days, beginning the medication during the first 24 hours post partum.

Engorgement and pain were prevented in 81.6 per cent of the patients with the use of Estan in the third group as compared with 55 per cent in the second group of individuals. With the use of testosterone in group one, these symptoms were always present.

No undesirable side effects were present as a result of the Estan therapy. Supportive measures other than codeine and aspirin for afterpains were not

employed. The patients were not limited as to the type and amount of fluid intake.

The conclusion is that a combination of estrogen and androgen (Estan) is of value in the prevention of lactation and engorgement of the breast in the puerperium. The higher dosage, namely, 2 tablets of Estan, three times a day for 5 days, should be the one employed.

While the results in our small study in general are good, it should be borne in mind that there are a certain number of patients who will not receive any benefit whatsoever, no matter what type of medication is employed.

I wish to express my appreciation to Dr. Edward C. Hughes for his support and assistance in preparing this survey. In addition I wish to express my gratitude to the Attending Staff, House Staff, and nursing personnel of Syracuse Memorial Hospital, and to Miss Nancy Cochrane, departmental secretary.

References

1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 5, Baltimore, 1950, Williams & Wilkins Company, p. 886.
2. Stricker, P., and Gruter, F.: Klin. Wchnschr. 8: 2322, 1929.
3. Reece, R. P., and Turner, C. W.: Proc. Soc. Exper. Biol. & Med. 34: 402, 1936.
4. Meites, J., and Turner, C. W.: Endocrinology 30: 719, 1942.
5. Riley, G.: Essentials of Gynecologic Endocrinology, Ann Arbor, Mich., 1948, Caduceus Press, p. 45.
6. Selye, H., Collip, J. B., and Thomson, D. L.: Endocrinology 18: 237, 1934.
7. Ribson, J. M.: Proc. Soc. Exper. Biol. & Med. 36: 153, 1937.
8. Kurzrok, R., and O'Donnell, C. P.: Endocrinology 23: 476, 1938.
9. Salter, N. T.: Textbook of Pharmacology, Philadelphia, 1952, W. B. Saunders Company, p. 527.
10. Kurzrok, R., Bates, R. W., Riddle, O., and Miller, E. G., Jr.: Endocrinology 18: 18, 1934.
11. Krantz, J. C., Jr., and Carr, C. J.: The Pharmacologic Principles of Medical Practice, ed. 2, Baltimore, 1951, Williams & Wilkins Company, p. 933.
12. Stewart, H. L., Jr., and Pratt, J. P.: Am. J. Obst. & Gynec. 41: 555, 1941.
13. Walsh, J. W., and Stromme, W. B.: Am. J. Obst. & Gynec. 47: 655, 1944.
14. Riley, G.: Essentials of Gynecologic Endocrinology, Ann Arbor, Mich., 1948, Caduceus Press, p. 45.
15. Greenblatt, R. B., Barfield, W. E., Garner, J. F., Calk, G. L., and Harod, J. P., Jr.: J. Clin. Endocrinol. 10: 1558, 1950.

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THE SHORT UMBILICAL CORD*†

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THE short umbilical cord is a complication of obstetrics which has received insufficient attention. In spite of the fact that this condition is common, the literature on the subject during the past ten years has been meager. The standard textbooks give it only brief mention. Less than a dozen articles on the subject have appeared in the medical journals since 1940; three in English, none in American publications; five of the articles are in foreign journals not available in the libraries in New York.

Because of the paucity of available information and the possibility that modern obstetric practice might improve the handling of this complication, I undertook the study of the short umbilical cord. The findings and conclusions warrant this report.

Literature

A brief résumé of the literature will serve to establish the current opinions concerning the short umbilical cord.

DeLee[1] states that cords may be either absolutely or relatively short. The latter are those which coil around the neck or extremities of the fetus one or more times and in this way become too short for the maintenance of the proper mechanism of labor. The short cord may lead to: (1) prolongation of the second stage of labor (the head descends with difficulty and recedes quickly as if being drawn back by a rubber band), (2) rupture of the umbilical cord, (3) tearing of the cord from the placenta, (4) tearing of the placenta from the uterus, (5) inversion of the uterus, (6) painful uterine contractions and secondary inertia.

DeLee concludes with the note that special treatment is seldom required because of the rarity of the condition.

Stander[2] states that in 25 to 30 per cent of all deliveries the child's neck will be encircled by one or more loops of cord. The danger to the fetus is not due to a drawing taut of the loop, but rather to the fact that the loop does not accommodate the neck as the child increases in size.

Titus[3] declares that the short cord may cause fatal asphyxia or delay in the descent of the presenting part. He points out that unusually long cords are more likely to become coiled about various parts of the fetus than are shorter cords.

McCormick[4] outlines the hazards of the short umbilical cord and observes that all of the complications are quite rare.

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*Thesis submitted to the faculty of the Graduate School of Medicine of the University of Pennsylvania, toward the requirements for the degree of Master of Medical Science for graduate work in Obstetrics and Gynecology.

†Read before a meeting of The Obstetrical Society of Philadelphia, April 2, 1953.

Hamilton[5] describes the mechanisms by which a cord around the neck may lead to fetal distress. Morgan[6] mentions the prolongation of labor and distress to the fetus which may result. Jaede[7] cites a case of intrauterine fetal death due to "strangulation of the umbilical cord." Zambonini[8] studied 10,295 umbilical cords and noted wide variations in length. The average cord measured 50 cm., the shortest 20 cm. Absolute shortness of the cord (less than 30 cm.) was present in 45 cases (0.43 per cent); 36 of these did not produce any complication during labor and delivery. Umbilical cords looped about some portion of the fetus were seen in 1,185 cases; in 1,166 these were around the neck; 11 fetal deaths occurred in this series, a mortality of 0.93 per cent.

Neto[9] has set forth several noteworthy observations. Most cases of short cord do not cause dystocia or preclude spontaneous delivery. Nevertheless, he reports five case histories, four with fatal outcome for the fetus.

From the cited literature the signs and symptoms of a short cord are the following: (1) delay in the second stage of labor, (2) failure of a normally presenting part to descend into a normal pelvic cavity, (3) recession of the presenting part at the end of each contraction, (4) persistently high presenting part or frank malposition, (5) disturbances in the fetal heart rate, e.g., a marked slowing, irregularity, and accentuation of the second sound during a contraction with delayed recovery of rate and rhythm between contractions, (6) passage of meconium in vertex presentations, (7) increased activity of the infant, (8) irregular, short, and painful uterine contractions, and (9) hypertonicity of the uterus.

Hamilton suggests the following maneuver as a diagnostic sign. If the head is high and the fetal heartbeat of good quality, push the head into the pelvis while listening to the fetal heart. A drop to 80 per minute or below with recovery to 120 per minute or more upon release of the head is presumptive evidence of a short cord.

Organization of Material

In the preparation of material for this report, I carefully followed the course and conduct of labor of all patients delivered at the Brooklyn Womens Hospital between July 1, 1948, and June 30, 1949. All cases presenting either absolute or relative shortening of the umbilical cord were studied. An equal number of similar cases, presenting no cord complications, were chosen as controls from the consecutive deliveries which occurred during the months of July and August, 1948.

The material was analyzed to obtain a comparison between the control series of cases and the "short cord" cases so as to elicit a relationship, if any, which might exist between the occurrence of a "short cord" and the following factors:

1. Parity.
2. Length of labor, first and second stages.
3. Type of delivery.
4. Umbilical cord complications.
5. Birth weights.

6. Cases showing fetal distress. Criteria used for determining distress were: (a) slowing of the fetal heartbeat, (b) passage of meconium in cephalic presentations.

7. Cases requiring resuscitation. It is considered normal that all infants receive (a) mouth suction to remove mucus, and (b) a few moments of oxygen inhalation. Cases which required more than this minimal amount of attention were considered to fall into the category of those requiring resuscitation. This procedure implies special efforts on the part of the physician, e.g., suction of the mouth and trachea, use of alternating positive and negative pressures for administering oxygen, and injection of drugs.

8. Stillbirths.

Results

During the 12 month period from July 1, 1948, to June 30, 1949, there were 1,525 deliveries at the Brooklyn Womens Hospital. Of these, 269 (17.6 per cent) presented the complication of the absolutely or relatively short umbilical cord. The results of the statistical analysis of these deliveries, as well as those of the control group are presented.

1. Parity.—

There were 118 primiparas and 151 multiparas in the "short cord" group as compared with 126 primiparas and 143 multiparas in the control group.

TABLE I. PARITY OF PATIENTS WITH SHORT UMBILICAL CORD AS COMPARED WITH CONTROL SERIES

PARITY	SHORT CORD	CONTROL
i	118	126
ii	96	89
iii	41	39
iv	7	10
v	4	2
vi	3	3

2. Length of Labor.—

A. First stage of labor: The average length of the first stage of labor for primiparas was 11¾ hours and for multiparas 7½ hours. In the control group the first stage was 12 hours and 6¾ hours, respectively.

B. Second stage of labor: Primiparas averaged 1¼ hours and multiparas ½ hour as compared with the control group of one hour and ½ hour, respectively.

TABLE II. LENGTH OF LABOR IN PATIENTS WITH SHORT CORD AND IN CONTROL SERIES

	SHORT CORD	CONTROL
Length of First Stage.—		
Primiparas	11¾ hours	12 hours
Multiparas	7½ hours	6¾ hours
Length of Second Stage.—		
Primiparas	1¼ hours	1 hour
Multiparas	½ hour	½ hour

3. Type of Delivery.—This is presented in Table III.

TABLE III. TYPE OF DELIVERY IN PATIENTS WITH SHORT CORD AND IN CONTROL SERIES

TYPE OF DELIVERY	SHORT CORD	CONTROL
Spontaneous	114	98
Low forceps	135	138
Midforceps	13	12
Manual rotations	15	14
Forceps rotations	18	14
Breech extractions	2	11
Version and extraction	1	0
Cesarean sections	4	10

4. Cord Complications.—

The types of cord complications found at delivery were as follows (Table IV). There were 247 cases in which the umbilical cord was entwined around the neck of the fetus, 13 cases around the body, 4 cases around the legs, and 12 cases of absolute shortness of the cord, i.e., a cord less than 30 cm. in length. No instance of a torn cord or detached placenta was found.

TABLE IV. FREQUENCY OF SPECIAL TYPES OF CORD COMPLICATION

NO. OF LOOPS	AROUND NECK	AROUND BODY	AROUND LEGS
1	207	8	2
2	30	5	2
3	7	0	0
4	3	0	0

5. Birth Weights.—

The birth weights of the infants are presented in Table V.

TABLE V. BIRTH WEIGHTS OF INFANTS IN PATIENTS WITH SHORT CORD AND IN CONTROL SERIES

BIRTH WEIGHTS	SHORT CORD	CONTROL
Under 5 pounds	7	12
5-6 pounds	35	31
6-7 pounds	90	96
7-8 pounds	93	92
Over 8 pounds	44	38

6. Fetal Distress.—

In the group of cases which presented short umbilical cords, 12 (4.46 per cent) had shown some type of fetal distress during labor. In the control group there were 9 cases (3.34 per cent) in which some type of fetal distress was evident.

7. Resuscitation.—

Seventeen newborn infants (6.32 per cent) in the group with short umbilical cords required resuscitation beyond that considered normal; in the control group ten cases (3.72 per cent) required a similar amount of resuscitation.

8. Stillbirths.—

In the group with cord complications there were three stillbirths (1.1 per cent) and in the control group there were seven (2.6 per cent).

Observations and Findings

Several observations may be drawn from the study:

1. The incidence of short umbilical cord was 17.6 per cent of 1,525 consecutive cases; 0.78 per cent were absolutely short, 16.8 per cent were relatively short.

2. Labor was not prolonged in either the first or second stage.

3. The incidence of operative deliveries was not increased; in fact in the "short cord" group there were twice as many deliveries, all spontaneous, which did not require anesthesia as compared with the control group.

4. The incidence of fetal distress during labor was increased in the "short cord" group.

5. Asphyxia neonatorum, requiring special resuscitation, was greater in the "short cord" group.

6. The stillbirth incidence was not increased.

Comment

The findings of this study agree in certain instances and disagree in others with the consensus of opinions in the literature. The general result is a clarification of the true position and importance of the short umbilical cord.

A. The frequency with which I have encountered the short umbilical cord, 17.6 per cent, falls between the only two figures I have found in the literature, namely, the 25 to 30 per cent of Stander and the 12 per cent of Zambonini. Absolute shortness of the cord in my series, 0.78 per cent, agrees approximately with the 0.43 per cent found by Zambonini.

It is clear, therefore, that the short cord is relatively common; so common, in fact, that its potential hazard has been practically neglected. This attitude of indifference may seem to be favored by the finding of this study that the progress of labor under normal conditions is not delayed or complicated by an undue incidence of operative interference. Indeed, contrary to many of the statements in the literature, I have found no justification for believing that a short umbilical cord causes slow cervical dilatation and nondescent of the presenting part.

B. This study confirms the experience of earlier authors that the short cord is associated with an increased incidence of fetal distress during labor and resuscitation after labor. If we are to attain a higher rate of salvage among infants with short cords, the obstetrician must be aware of the relatively high incidence of this condition, and be alert to institute early the prophylactic measures appropriate to the circumstances of the labor at the time that fetal distress is first noted.

If the degree of cervical dilatation and the station of the presenting part permit immediate delivery by operative measures, this should be done as soon as fetal distress is discovered. This method of management demands an expert obstetrician. It abruptly terminates all further ill effects produced by the "bearing down" forces and the descent of the presenting part in a fetus with a short umbilical cord. If the fetus is not ready for delivery immediately

after the observation of distress, I believe that caudal or low spinal analgesia is indicated. The efficacy of this measure depends on the fact that further cervical dilatation can occur without harm to the fetus. The "bearing down" reflex is eliminated without serious depression of the uterine contractions. Thus, the cervix may continue to dilate under the influence of the uterine contractions but the extrauterine forces which contribute to the descent of the presenting part are not brought into play. Consequently, the fetus with a short cord avoids the most damaging phase of labor. Furthermore, the use of caudal or low spinal analgesia eliminates the need for narcotics, barbiturates, or general anesthetics at the delivery of a fetus already subjected to the asphyxial hazard associated with a short umbilical cord.

When caudal or low spinal analgesia has been started at the proper time for the relief of pain in an apparently normal case, the failure of the presenting part to descend may lead the obstetrician to suspect a short umbilical cord before the appearance of fetal distress. With a short umbilical cord, though the presenting part may fail to descend, the cervix dilates normally. If the examiner forces the presenting part down by external pressure during a uterine contraction it is felt to descend well below the spines, but promptly ascends with release of the extrauterine force exerted by the examiner. Furthermore, auscultation of the fetal heart during this induced descent of the presenting part reveals evidence of an anoxic influence on the rate or rhythm. The provisional diagnosis of a short umbilical cord is justified under these circumstances and operative delivery is in order as soon as the cervix and station permit.

Summary

1. During the 12 month period from July 1, 1948, to June 30, 1949, there were 1,525 deliveries at the Brooklyn Womens Hospital. Of these, 269 presented the complication of the short umbilical cord, an incidence of 17.6 per cent.

2. There was no significant increase in the duration of the first or second stage of labor.

3. There was no difference in the types of deliveries in the study group as compared to the control group, i.e., no added operative interference was required.

4. The type of anesthesia used played no part in the outcome of the cases. A suggestion regarding the use of continuous caudal and low spinal analgesia is made.

5. The incidence of fetal distress and the need for resuscitation of the newborn are increased in the "short cord" group of cases.

6. Shortening of the umbilical cord does not seem to be a major contributing cause of stillbirth.

References

1. DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1947, W. B. Saunders Company.
2. Stander, H. J.: Textbook of Obstetrics, ed. 3, New York, 1945, D. Appleton-Century Company.
3. Titus, P.: The Management of Obstetric Difficulties, ed. 3, St. Louis, 1945, The C. V. Mosby Company.

4. McCormick, C. O.: Pathology of Labor, the Puerperium and the Newborn, St. Louis, 1944, The C. V. Mosby Company.
5. Hamilton, J.: Clin. J. 76: 103, 1947.
6. Morgan, J.: Brit. M. J. 2: 820, 1948.
7. Jaede, C. H.: M. J. Australia 2: 23, 1946.
8. Zambonini, A.: Riv. ital. di ginec. 28: 60, 1945.
9. Neto, P.: Arq. brasil. de cir. e ortop. 12: 260, 1944.

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Discussion

DR. S. LEON ISRAEL.—Dr. Rosen has enlightened us concerning an uncommon, though dangerous, threat to fetal life. Reviewing for us the incidence, signs, and symptoms of the short umbilical cord, he reminds us that we must think of such a diagnostic possibility in the presence of intrapartal signs of fetal distress. The fact that he encountered no stillbirths in his experience with 12 absolutely short and 257 relatively short cords is fortunate indeed. Had any of these 269 short cords had a velamentous insertion as well, there would undoubtedly have been at least one fetal death. As pointed out to this Society two years ago by the late Dr. W. Edward Torrey, Jr., the combination of short cord and velamentous insertion, a variant of vasa previa, results in traction laceration of the umbilical vessels and eventuates in fetal death from hemorrhage.

The concept of an absolutely short cord is easy to comprehend because it may be proved by measurement. On the other hand, the diagnosis of relatively short cord may be based on a false premise. The fact that the cord is found looped around a part of the baby's body does not necessarily indicate that it is short. On the contrary, as Dr. Rosen indicated, such looping may be the consequence of an especially long cord. It is the tautness of the loop which makes the cord relatively short and the condition serious. It may be possible to recognize the relatively short cord roentgenologically during labor, particularly since the fetal neck is the part usually looped. Angulation of the head in all instances of its failure to engage in labor should heighten suspicion. Such an intrapartal diagnosis has been successfully made 40 times by Dr. Paul Bishop, radiologist to the Pennsylvania Hospital, by excluding all other causes of failure of fetal descent and by visualizing high implantation of the placenta. However, neither roentgenographic aid nor Hamilton's pressure test can be of diagnostic value unless applied. This will not be done, as Dr. Rosen's report emphasizes, unless the obstetrician thinks of the possibility of short cord. The 1 per cent mortality of babies born with cords wound around the neck indicates that the problem is not purely academic. Dr. Rosen has brought us face to face with the necessity of accurate observation of the fetal heart rate during labor, compelling us to recall the presence of unknown factors which make it impossible to minimize the conduct of apparently normal labor.

LEVELS OF PROGESTERONE IN SYSTEMIC PLASMA DURING THE FIRST TRIMESTER OF HUMAN PREGNANCY*

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THE functional relationship of the corpus luteum to pregnancy has intrigued investigators for fifty years. The need for progesterone in rabbit pregnancy was indicated by Corner,[6] Corner and Allen,[7, 8] and Allen and Heckel.[1] Zeiner[25] and Kelsey and Meyer[19] showed that the continuation of pregnancy in the rat depends on the presence of corpora lutea. However, Pratt,[23] Corbet,[5] Jones and Weil,[17] and Melinkoff[21] have reported cases of the removal of the functional corpora lutea from women at the end of approximately the first month of gestation with completion of normal pregnancy. Hartman[12, 13] has ovariectomized the rhesus monkey early in pregnancy without interruption of gestation.

Attempts have been made further to understand the metabolism of progesterone during human pregnancy by the measurement of pregnanediol in the urine. Many investigations indicated that the concentration of pregnanediol in the urine increases as pregnancy advances. From this observation, it was often assumed that the need for progesterone increases as the embryo develops.

This inference supported clinical administration of progesterone in pregnancy, primarily in threatened or habitual abortion. Kane,[18] Elden,[9] Mason,[20] Hertig and Livingstone,[15] Bishop and Richards,[2] and others recommended the use of progesterone in the treatment of abortion. However, Colvin, Bartholomew, Grimes, and Fish,[4] after discussing causes of abortion, suggested that only approximately 3.9 per cent of the abortions they studied could theoretically have been prevented by "hormone" therapy.

A direct method of study of progesterone has been made possible with the development by Hooker and Forbes[16] of a sensitive bio-assay technique for the quantitative estimation of this hormone. Determinations by Forbes[10, 11] revealed progesterone levels ranging from 0 to 3 micrograms per cubic centimeter of plasma in human and monkey pregnancy, and from 1 to 8 μg per cubic centimeter of plasma in the pregnant mouse. Neher and Zarrow,[22] using the Hooker-Forbes technique, observed that in the ewe the levels increased through pregnancy to about 12 μg per cubic centimeter of plasma. However, Haskins[14] and Butt, Morris, Morris, and Williams[3] reported negative results from assay of human pregnancy blood for progesterone. These authors used ultraviolet spectroscopy and chromatographic-polarographic techniques, respectively, in their investigations.

*The investigation was aided by a grant from the James Hudson Brown Memorial Fund of Yale University. The report was condensed from a thesis submitted in partial fulfillment of the requirements for the M.D. degree at Yale University.

Materials and Methods

Forty-eight 1 c.c. blood samples were obtained from 46 women, in all instances between 6 and 17 weeks after the last menstrual period. The samples obtained were either processed at once or were refrigerated until the plasma could be precipitated.

The intrauterine assay technique of Hooker and Forbes[16] was used for the determinations reported in this paper. The samples were first assayed for "free" progesterone, that is, the progesterone circulating in the plasma as the ether- and acetone-soluble steroid. The progesterone apparently attached to protein in the plasma ("bound" progesterone) was determined on 21 random samples.

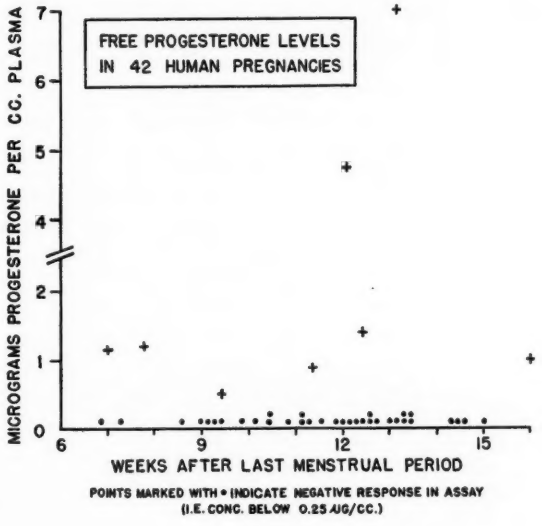

Fig. 1.

Results

Of the 46 donors, 34 were proved pregnant by their subsequent histories. The charts of 9 women were not available. Because three charts failed to record a birth, these patients were presumed also not to be pregnant. Thus data are missing for 12 patients. Of the 34 patients with proved pregnancies, 22 went to term, 2 delivered prematurely, and 10 aborted. Nine of the abortions were spontaneous, and one was self-induced. Serologic tests in all cases were negative. There were 10 positive responses, 8 of them below 2.0 µg/c.c. plasma, one of 4.8 µg/c.c. plasma, and one of 7.0 µg/c.c. plasma. No correlation between these positive responses and other factors was apparent. No progesterone was detected in the remaining blood samples. Bound progesterone levels were determined on 21 random samples; all gave negative reaction to the assay, that is, the progesterone content was below the minimal detectable level of 0.2 µg/c.c. plasma.

Fig. 1 summarizes the relationship between the positive and negative responses and time of pregnancy. Some assay results could not be included because the date of the last menstrual period was not known. These results included two positive responses with levels of 1.59 and 0.35 µg/c.c. plasma.

Comment

At the beginning of this study, it was suspected that possibly some difference in progesterone levels in normal and aborting pregnancies could be established. Also, it was thought that a relationship might exist between time of day and circulating progesterone level. However, since there were only 10 positive responses and since 3 of these were in cases of abortion, there appears to be no evidence that abortion was due to a deficiency of the hormone. Similarly, as seen from the graph, there seems to be no smooth curve relation between progesterone level and time of pregnancy.

Experiments mentioned above have shown quite conclusively that progesterone is needed during pregnancy in the rabbit and rat and that high levels of the hormone occur during pregnancy in the mouse. Neher and Zarrow[22] showed that in the pregnant ewe the blood progesterone level increases progressively up to 13 μg per cubic centimeter of serum at term. In contrast to these lower animals, women and monkeys, as has been mentioned, may be able to continue pregnancy following ovariectomy performed after perhaps the first four weeks of gestation. In primates the secretion of the corpus luteum is generally believed to be necessary for the preparation of the endometrium, migration of the ovum, and nourishment of the ovum before implantation, but the role of this hormone in pregnancy from this point on is uncertain. If progesterone is necessary in human pregnancy after the first month, it is possible that placental progesterone secretion accounts for the noneffect of ablation of the ovaries. Salhanick, Noall, Zarrow, and Samuels[24] reported the isolation of progesterone from the human placenta; the hormone was identified by the Hooker-Forbes assay technique.

All investigators have been impressed with the very minute quantities of progesterone detected in human pregnancy blood. This discovery was received with some surprise, for the assumption, based on pregnanediol excretion curves, had been that progesterone levels increased progressively during pregnancy. One can postulate that the amount of progesterone necessary for maintenance of pregnancy does, in fact, increase and that secretion of progesterone by the ovary, placenta, or adrenal gland meets this demand. If so, in order to explain the low blood levels of progesterone one is forced to conclude that the progesterone acts and is then immediately metabolized. The alternative hypothesis is that progesterone may be of less importance in pregnancy than has been generally believed.

The volume of literature suggesting the use of progesterone for treatment of threatened abortions, habitual abortion, premature deliveries, retroversion of the uterus, etc., is impressive. However, as Colvin, Bartholomew, Grimes, and Fish[4] have mentioned, most abortions seem to be caused by a diseased or deficient conceptus. The death of the embryo or fetus often occurs about six weeks prior to the onset of the symptoms; in such cases, progesterone therapy is futile. Although, according to these authors, approximately 3.9

per cent of the abortions studied could theoretically have been prevented by "hormone" therapy, it is difficult, if not impossible, to recognize such cases before abortion occurs.

Summary and Conclusions

The Hooker-Forbes assay was used to determine plasma progesterone levels in 48 samples of blood obtained from 46 women between the sixth and seventeenth weeks after the last menstrual period. There were 38 negative responses and 10 positive responses, with levels for the latter predominantly below 2.0 μg per cubic centimeter of plasma. The results confirm those of previous investigations.

Until the exact mechanism of progesterone action in pregnancy is known, no rational progesterone therapy can be employed in the treatment of spontaneous or habitual abortion.

References

1. Allen, W. M., and Heckel, G. P.: Am. J. Physiol. **125**: 31, 1939.
2. Bishop, P. M. F., and Richards, N. A.: Brit. M. J. **2**: 130, 1950.
3. Butt, W. R., Morris, P., Morris, C. J. O. R., and Williams, D. C.: Biochem. J. **49**: 434, 1951.
4. Colvin, E. D., Bartholomew, R. A., Grimes, W. H., and Fish, J. S.: Am. J. Obst. & Gynec. **59**: 1208, 1951.
5. Corbet, R. M.: Irish J. M. Sc., p. 520, August, 1932.
6. Corner, G. W.: Am. J. Physiol. **86**: 74, 1928.
7. Corner, G. W., and Allen, W. M.: Am. J. Physiol. **88**: 326, 1929.
8. Corner, G. W., and Allen, W. M.: Am. J. Physiol. **88**: 340, 1929.
9. Elden, C. A.: Am. J. Obst. & Gynec. **35**: 648, 1938.
10. Forbes, T. R.: Anat. Rec. **100**: 29, 1948.
11. Forbes, T. R.: Endocrinology **49**: 218, 1951.
12. Hartman, C. G.: Proc. Soc. Exper. Biol. & Med. **48**: 221, 1951.
13. Hartman, C. G., and Corner, G. W.: Anat. Rec. **98**: 539, 1947.
14. Haskins, A. L., Jr.: Proc. Soc. Exper. Biol. & Med. **73**: 439, 1950.
15. Hertig, A., and Livingstone, R. A.: New England J. Med. **230**: 797, 1944.
16. Hooker, C. W., and Forbes, T. R.: Endocrinology **41**: 158, 1947.
17. Jones, H. W., and Weil, P. G.: J. A. M. A. **111**: 519, 1938.
18. Kane, H. F.: Am. J. Obst. & Gynec. **32**: 110, 1936.
19. Kelsey, R. C., and Meyer, R. K.: Proc. Soc. Exper. Biol. & Med. **75**: 736, 1950.
20. Mason, L. W.: Am. J. Obst. & Gynec. **44**: 630, 1942.
21. Melinkoff, E.: Am. J. Obst. & Gynec. **60**: 437, 1950.
22. Neher, G. M., and Zarrow, M. X.: Anat. Rec. **108**: 556, 1950.
23. Pratt, J. P.: Endocrinology **11**: 195, 1927.
24. Salhanick, V. A., Noall, M. W., Zarrow, M. X., and Samuels, L. J.: Science **115**: 708, 1952.
25. Zeiner, F. N.: Endocrinology **33**: 239, 1943.

ANEURYSM OF THE SPLENIC ARTERY IN PREGNANCY

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ANEURYSM of the splenic artery is a rare entity which has been reported in the literature as single case reports since Crisp's[2] original description in 1847. Since that time there have been approximately 152 cases reported[2] and, of these, 27 have been associated with pregnancy.

It is the purpose of this paper to report a case of aneurysm of the splenic artery in pregnancy and to present a complete analysis of all the cases reported in the literature (Table I).

Case Report

I. H., a 41-year-old white woman, gravida ii, para i, had an uneventful first pregnancy ten years previously and she had no complications during her second pregnancy until the latter part of the ninth month. The patient was well until 5 P.M. on Sept. 30, 1951, when she suddenly developed severe epigastric pain accompanied by vomiting. The vomiting persisted and at 2 A.M., Oct. 1, 1951, she again developed severe epigastric pain followed by collapse. Examination revealed marked epigastric pain and left upper quadrant tenderness to pressure but there were no signs of labor. Before definitive replacement therapy for shock could be instituted, the patient died.

Postmortem examination revealed the abdomen to contain a uterus at term without evidence of any tears or rupture. The abdominal cavity contained 3,000 c.c. of unclotted blood and the lesser peritoneal cavity contained blood which was clotted. The tail of the pancreas was completely covered by this large clot. The splenic vein was normal as was the splenic artery throughout its course except at a point 1 cm. from the hilum of the spleen where there was a large, bulbous dilatation of the artery with a very thin wall. At the distal end of the dilatation there was a definite perforation. The aneurysmal sac measured 2 cm. in length and the perforation measured 0.5 cm. in cross section (Fig. 1). The spleen was normal in size and weight. Longitudinal sections of the splenic artery proximal to the aneurysm on microscopic examination revealed the intima, inner elastic membrane, media, and adventitia to be normal. However, there was an abrupt change at the juncture with the aneurysm where there was an accumulation of fibers in a concentric layer, some longitudinal fibers and a marked increase in fibrous tissue (Fig. 2). The wall of the aneurysm proper was composed of a very thin layer of friable, fibrous connective tissue arranged in a longitudinal fashion along with a few smooth-muscle fibers. The inner elastic membrane appeared to be very thin in some areas and thickened in others, revealing definite evidence of congenital malformation.

Diagnosis

In the cases reviewed, the outstanding symptom was severe abdominal pain. Twelve of the authors described the pain as epigastric and 4 as pain in the left hypochondrium. In one case, the patient also had pain in the left shoulder and in two the pain radiated to the back. Ten of the patients had severe vomiting while in 2 of these cases vomiting was the initial symptom.

The initial sign in 2 cases was collapse with signs and symptoms of shock. On physical examination, most authors have described abdominal tenderness and in 10 cases the tenderness was definitely localized to the epigastrium. Four patients had dullness to percussion in the left side and 4 authors described the uterus as being soft. All of the patients eventually developed signs and symptoms of shock. In 7 cases, a diagnosis of premature separation of the placenta was considered, uterine rupture was the primary diagnosis in 5 cases, while the majority of the remaining cases were diagnosed as intra-abdominal hemorrhage.

The initial clinical picture, therefore, is usually that of severe epigastric or left upper quadrant pain of sudden onset which may radiate to the back or either arm, often accompanied by vomiting. Within a short time, this is followed by the signs and symptoms of shock with no external evidence of hemorrhage. There is usually severe epigastric tenderness with dullness to percussion in the left upper quadrant of the abdomen.

Fig. 1.—Gross specimen of aneurysm of the splenic artery. Arrow indicates aneurysmal sac which has been opened.

In the case described by McLeod,[14] the patient presented this typical picture of severe internal hemorrhage. A laparotomy was performed five hours after the onset of the first symptom and splenectomy was performed with survival of the patient. The patient delivered a macerated fetus five days after surgery and subsequently she had a normal pregnancy. In the case described by Gillam,[8] the patient presented the usual signs and symptoms associated with rupture of a splenic aneurysm. A diagnosis of premature separation of the placenta was made and labor induced but the fetus was stillborn. The patient continued to experience epigastric pain after delivery but this symptom gradually subsided and she had a normal postpartum course. She was discharged from the hospital but two weeks after the onset of the initial symptoms she again developed severe epigastric pain and collapsed immediately following a bowel movement. Laparotomy was performed and a cure obtained after splenectomy. In this case, there was a definite latent

TABLE I

CASE AUTHOR YEAR	AGE GESTATION	SYMPTOMS AND FINDINGS	DIAGNOSIS	PATHOLOGIC FINDINGS AND PATHOGENESIS	LAPAROTOMY, RESULTS REMARKS
1. Nodes 1900	33 Gravida vi Term	"Convulsion" None mentioned	None	Aneurysm at hilum by spleen 3 by 5 by 3 cm. located at bifurcation	None. Death in ¼ hour. Aneurysm ruptured immediately after delivery. Fetus dead
2. Smith 1911	35 ? 9 months	Abdominal pain No signs of labor Others not mentioned	None	Rupture at bifurcation of artery Congenital. Question of endocarditis and embolism	None. Death in 12 hours. Washed clothes and moved washer day before demise. Fetus dead
3. Wesenberg 1912	32 Gravida iv 33 weeks	Severe abdominal and back pain Abdomen tender over liver area. Abdomen distended and uterus tense and tender	Premature separation of placenta	Aneurysm 5 by 3 cm.	None. Death in 9 hours. Lifted laundry. Labor induced and fetus dead
4. Lundwall 1923	29 Gravida i Term	Vomiting and severe epigastric pain Upper abdomen tender and uterus soft	Premature separation of placenta Suspected ruptured spleen or varix	Aneurysm near the celiac axis 2 cm. in diameter	Supracervical amputation of uterus and on exploration of upper abdomen source of bleeding could not be located. Death in 48 hours. Fetus dead
5. Yolland 1925	27 Gravida i 18 weeks	Severe pain left hypochondrium and severe vomiting Dullness over left side	None	Small aneurysm along the main artery	None. Death in 12 hours. Fetus dead
6. Saenger 1926	40 Gravida ix 33 weeks	Severe epigastric pain Tenderness in upper abdomen	Spontaneous rupture of uterus in a case of placenta accreta	Aneurysm the size of a hazelnut	Bleeding point was packed. Death 2½ hours after admission. Fetus dead
7. Van Rooy 1927	38 Gravida xi Term	Severe left upper quadrant pain and vomiting None mentioned	Incomplete rupture of the uterus. Internal hemorrhage	Two aneurysms of the splenic artery, the larger of which ruptured	Being prepared for laparotomy. Death in 9 hours. Fetus dead
8. Remmelts 1928	38 Gravida ix Term	Severe abdominal pain Uterus soft	Internal hemorrhage with possible ruptured uterus	Aneurysm 2 cm. in diameter	None. Death in 6 hours. Fetus dead
9. Mayer 1928	27 Gravida iii Term	Severe abdominal pain None mentioned	Thought picture was due to sedatives	Aneurysm 3 cm. in diameter at bifurcation	None. Death 1½ hour after delivery. Living baby delivered with forceps
10. Bauer 1932	24 ? 8 months	Epigastric pain Uterus soft. No bleeding from cervix	Possible intra-abdominal hemorrhage	Aneurysm near hilum 1 cm. in diameter Congenital	None. Death in 8 hours. No evidence of labor. Fetus dead
11. Bohler 1933	27 ? 7 months	Epigastric and left upper quadrant pain Abdomen markedly distended	Ruptured spleen	Aneurysm near hilum	None. Death in 15 hours. Lifted basket of potatoes. Fetus dead

12. Heuveldop 1934	28 Gravida ii 35 weeks	Sudden collapse None mentioned	None	Aneurysm near hilum size of walnut Mycotic	None. Death in 1 hour. Going to movies. Fetus dead
13. Sered 1935	30 Gravida iii Term	Epigastric, left upper quadrant, and left shoulder pain Epigastric tenderness and rigidity. Uterus soft	Ruptured viscus. Intra-abdominal hemorrhage	Aneurysm of midartery 1½ cm. in diameter Probably congenital	Low cervical cesarean section. Bleeding point could not be located. Death in 18 hours. Living baby
14. Ostling 1938	21 Gravida i 7 days post partum	Severe epigastric pain and vomiting Abdomen soft. Uterus tender	Cholelithiasis. Pulmonary infarction	Aneurysm size of fist 4 cm. from hilum	None. Living baby delivered 7 days before death. Developed thrombophlebitis
15. Guy 1939	25 ? 5 months	Pain across upper abdomen and vomiting Not mentioned	Ruptured ectopic pregnancy	Aneurysm 2 cm. in diameter at hilum Embolic	None. Death in 2½ hours. Fetus dead
16. McLeod 1940	22 Gravida i 28 weeks	Severe vomiting and pain in upper abdomen Tenderness in epigastrium	Concealed accidental hemorrhage	Aneurysm of small branch of artery near hilum	Splenectomy performed. Five days later delivered macerated fetus and had normal subsequent pregnancy
17. Lennie 1942	30 Gravida iii 32 weeks	Vomiting and severe pain in upper abdomen Tenderness and distention of epigastrium. Uterus firm and tender	Internal hemorrhage	Small false aneurysm of the midartery Congenital	None. Death in 6 hours. Dead fetus
18. Lennie 1942	30 Gravida i 31 weeks	Pain in abdomen radiating to back Generalized abdominal tenderness and resistance with dullness in the left side	Concealed accidental hemorrhage and later intra-abdominal hemorrhage	Saccular aneurysm 2 cm. in diameter located 8 cm. from the spleen	Packed after source of bleeding could not be found. Death in four days. Vomiting continued. Relapse third postoperative day and expired
19. Gillam 1942	26 ? Term	Severe epigastric pain and vomiting Generalized abdominal tenderness and resistance with dullness in the left side	Torsion of omentum and later intraperitoneal hemorrhage	No definite aneurysm was located	Splenectomy was performed and cure resulted. Initially labor was induced and dead fetus was delivered. She again developed pain immediately after bowel movement and was operated upon 16 days after onset of initial symptoms and four hours after recurrence of symptoms

TABLE I.—CONT'D

CASE AUTHOR YEAR	AGE GESTATION	SYMPTOMS AND FINDINGS	DIAGNOSIS	PATHOLOGIC FINDINGS AND PATHOGENESIS	LAPAROTOMY, RESULTS REMARKS
20. Danforth 1945	28 Gravida iv 7 months	Severe upper abdominal pain No abnormalities	Premature separation of placenta	Aneurysm 1.5 cm. in diameter Congenital	Vaginal hysterotomy performed and dead fetus delivered. Death in 12 hours
21. Cosgrove 1947	29 ? 5 months	Generalized abdominal pain Upper abdominal tenderness with dullness in left flank	None	Aneurysm near hilum 4 cm. in diameter	None. Death in 10 hours. Fetus dead
22. Cosgrove 1947	23 ? 16 hours post partum	Syncope and weakness Tenderness in epigastrium	None	Two aneurysms near hilum each measuring 2.5 cm. in diameter Congenital	None. Death in 12 hours. Fetus dead
23. Ogden 1948	25 Gravida ii 35 weeks	Sharp pain in left hypochondrium Uterus tense and tender	Premature separation of placenta	No definite aneurysm described	Cesarean section performed and macerated fetus delivered. Patient died five days after onset of symptoms and three days postoperatively
24. Sheehan 1948	32 Gravida iii 36 weeks	Abdominal pain and vomiting Abdomen slightly tender and tense	Intra-abdominal catastrophe	Small aneurysm of splenic artery	Classical cesarean section was performed and at time of section patient's condition was critical, hence vessels were not explored. Death in 33 hours
25. Chalmers 1949	26 Gravida ii 39 weeks	Severe abdominal pain None mentioned	Intra-abdominal hemorrhage	Aneurysm 3 by 2 by 1 cm. at bifurcation with rupture at point most remote from artery	None. Death in 9 hours. Fetus dead
26. DeVink 1950	32 Gravida ii 8 months	Upper abdominal and right shoulder pain Uterus tender	Premature separation of placenta	Aneurysm of splenic artery Congenital	None. Death in 7 hours. Doing housework. Fetus dead
27. Tennent 1950	36 Gravida ix 6 months	Pain in left hypochondrium and both thighs None mentioned	Ruptured uterus	Three small aneurysms the largest of which ruptured Congenital	None. Death in 8 hours. Fetus dead
28. Tomsykoski 1953	41 Gravida ii Term	Severe epigastric pain and vomiting Epigastric tenderness	Possible ruptured uterus	Aneurysm 2 cm. in diameter near hilum with perforation at point most remote from artery Congenital	None. Death in 10½ hours. Fetus dead

period of two weeks; the initial bleeding was probably confined to the lesser peritoneal sac while, in the second episode two weeks after the onset of the initial symptoms, the bleeding was into the general peritoneal cavity. In both cases, a diagnosis of internal hemorrhage was entertained and splenectomy performed as soon as possible after the diagnosis had been established, resulting in cure in both instances. It is therefore apparent that in cases presenting the signs of internal hemorrhage, rupture of an aneurysm of the splenic artery should be considered and corrective measures instituted immediately. In the case described by Gillam, there was a latent period of two weeks after delivery. In patients manifesting a latent period between episodes of bleeding where an aneurysm of the splenic artery is postulated, such as the case described by Gillam, aortography is indicated since Berger and associates[2] have shown that the aneurysm can be diagnosed by this method.

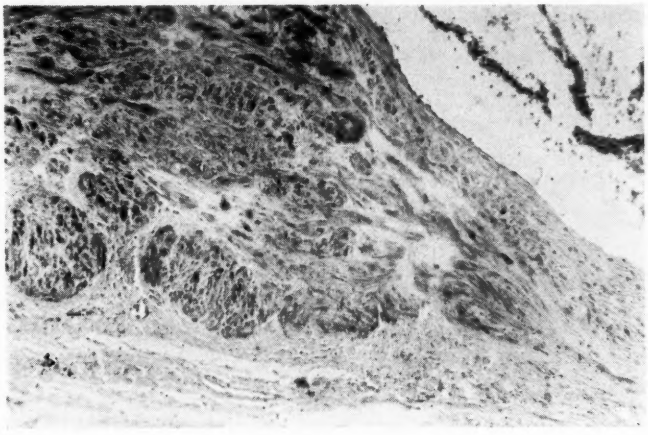

Fig. 2.—Low-power view of juncture of aneurysm with artery. Note the accumulation of muscle fibers in concentric layers with increase in fibrous tissue and the wall of the aneurysm which is composed of a thin layer of fibrous connective tissue arranged longitudinally along with a few smooth-muscle fibers.

Pathogenesis

Definite mention concerning the number of pregnancies was made in 22 cases and, of these, 6 were in primigravidas and 16 in multiparas. In 11 of the cases, the authors felt that the aneurysms were congenital in origin. Heuveldop[10] described degeneration of the media and postulated an old mycotic aneurysm; Guy[9] felt that the aneurysm was embolic secondary to subacute bacterial endocarditis and in the case described by Smith[22] an embolic phenomenon was considered. In a review of 63 cases of aneurysm of the splenic artery, Cosgrove, Watts, and Kaump[5] found that 37 of the cases were explained on an arteriosclerotic basis, 12 on a mycotic basis, 9 on a congenital basis, and 5 were classified as miscellaneous. Thus it is apparent that, in the cases associated with pregnancy, not one case was attributed to arteriosclerosis and in practically all of the cases in which the authors specified the aneurysms were explained on a congenital basis. This is most likely explainable by the difference in age groups of the two series. The fact remains,

however, that there was a history of some type of exertion in 7 of the cases described and, in addition to strain, the increase in intra-abdominal pressure associated with pregnancy must be considered. Endocrine changes in pregnancy have been mentioned as possible etiological factors by some authors.[5, 11]

Treatment

The only possibility of survival in cases of rupture of an aneurysm of the splenic artery lies in immediate surgical correction by splenectomy or ligation of the splenic artery. In 4 cases, death occurred within a two and one-half hour period after the onset of symptoms, making surgical treatment almost impossible. On the other hand, the remainder of the patients lived as long as six hours to two weeks from the onset of the first symptom to the time of death or operation and cure. Laparotomy was performed in 6 cases with survival of 2 of the patients following splenectomy. In the remaining 4 cases in which the bleeding source could not be located and definitive surgery could not be performed, the patients succumbed.

Summary

A case of rupture of an aneurysm of the splenic artery in pregnancy has been presented along with a review of the cases reported in the literature. The diagnosis, pathogenesis, and treatment of aneurysm of the splenic artery in pregnancy have been discussed and, in conclusion, it may be stated that early diagnosis and surgical correction are imperative for survival.

We wish to express our appreciation to Miss Marie Kerwin, medical librarian, for her assistance in securing data used in the preparation of this article and to Dr. Aronowitz for translating the foreign articles.

References

1. Bauer, C. P., and Appelbach, C. W.: Am. J. Obst. & Gynec. 24: 450, 1933.
2. Berger, J. S., Forsee, J. H., and Furst, J. N.: Ann. Surg. 137: 108, 1953.
3. Bohler, E.: Bull. Soc. d'obst. et de gynéc. 22: 707, 1933.
4. Chalmers, J. A.: Brit. J. Surg. 37: 86, 1949-50.
5. Cosgrove, G. E., Watts, J. C., and Kaump, D. H.: Am. J. Clin. Path. 17: 372, 1947.
6. Danforth, W. C.: Am. J. Obst. & Gynec. 50: 753, 1948.
7. DeVink, L. P. H. J., and Van Der Linde, H. M.: Tydschr. v. Geneesk. 94: 15, 1950.
8. Gillam, J. F. E.: Brit. M. J. 1: 69, 1942.
9. Guy, C. C.: Surgery 5: 602, 1939.
10. Heuveldop: Zentralbl. f. allg. Path. u. path. Anat. 61: 277, 1934-1935.
11. Lennie, R. A., and Sheehan, H. L.: J. Obst. & Gynaec. Brit. Emp. 49: 426, 1942.
12. Lundwall, K., and Godl, A.: Arch. f. Gynäk. 118: 177, 1923.
13. Mayer, E.: Zentralbl. f. Gynäk. 52: 754, 1928.
14. McLeod, D., and Maurice, T.: Lancet 1: 924, 1940.
15. Nodes, J. D. S., and Hinds, F.: Tr. Obst. Soc. London 42: 305, 1900.
16. Ogden, J. K.: Brit. M. J. 1: 389, 1948.
17. Ostling, K.: Acta obst. et gynec. Scandinav. 18: 444, 1938.
18. Remmelts, R.: Zentralbl. f. Gynäk. 52: 167, 1928.
19. Saenger, H.: Zentralbl. f. Gynäk. 50: 1324, 1926.
20. Sered, H., and Steiner, L. M.: Am. J. Obst. & Gynec. 29: 606, 1935.
21. Sheehan, H. L., and Falkiner, N. M.: Brit. M. J. 2: 1105, 1948.
22. Smith, H. B. W.: Brit. M. J. 1: 83, 1911.
23. Tennent, R. A., and Starritt, A.: Glasgow M. J. 31: 465, 1950.
24. Van Rooy, A. H. M. J.: Nederl. maandschr. v. geneesk. 14: 507, 1927.
25. Wesenberg, W.: Zentralbl. f. Gynäk. 118: 177, 1923.

INTERSTITIAL PREGNANCY

A Survey of 45 Cases

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ALTHOUGH development of a fertilized ovum within the interstitial portion of a Fallopian tube is the least frequent variety of tubal gestation, its occurrence is far from rare. The gravity of this condition is generally recognized,[1-4] but except for occasional case reports interstitial pregnancies as a group have received little attention in the literature. The picture is somewhat confused by interchangeable use of the terms "cornual" pregnancy and "angular" pregnancy. The former term more properly designates gestation within a rudimentary horn of a uterus and should be reserved for that condition. "Angular" pregnancy was introduced by Kerr and Anderson[5] in 1934 to describe an interstitial pregnancy which has developed adjacent to, or at the junction of, tubal and uterine mucosa, wherein the gestation sac eventually is extruded into the uterine cavity, often with continued growth of the embryo to term.

In view of the rarity of early diagnosis and the reported high mortality attendant upon rupture of an interstitial pregnancy, it seemed desirable to study 45 cases which have occurred in recent years at Kings County Hospital and the Jewish Hospital of Brooklyn. Since the majority of previously published reports antedate the widespread application of modern surgical principles and techniques, a re-evaluation of the incidence, clinical picture, prognosis, and management of interstitial pregnancy in the light of our present knowledge appears to be indicated.

As may be seen in Table I, there were 544 cases of ectopic pregnancy treated at Kings County Hospital from January, 1941, through March, 1953, of which 29 were interstitial pregnancies, an incidence of 5.3 per cent. Twenty-six of the patients were Negroes and 3 were white. Sixteen additional cases of interstitial pregnancy out of a total of 400 extrauterine pregnancies were treated at the Jewish Hospital of Brooklyn in the 18 year period from 1935 to 1953, an incidence of 4 per cent. Only 5 patients of this latter group were Negro women, the remaining 11 being white. Thus, out of a total of 944 ectopic gestations there were 45 cases of interstitial pregnancy, an over-all incidence of 4.7 per cent. Most reported statistics place its incidence at from 1.1 per cent to 6.3 per cent of all extrauterine pregnancies (Table II). In this entire series of interstitial pregnancies there was only one death, a mortality rate of 2.2 per cent (Table I).

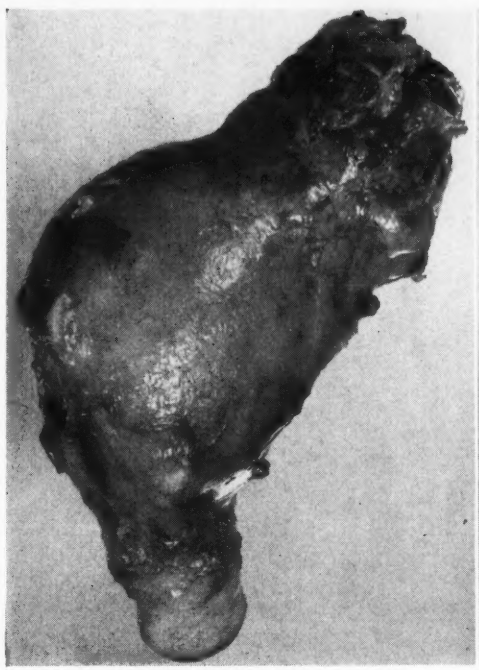

Fig. 1.

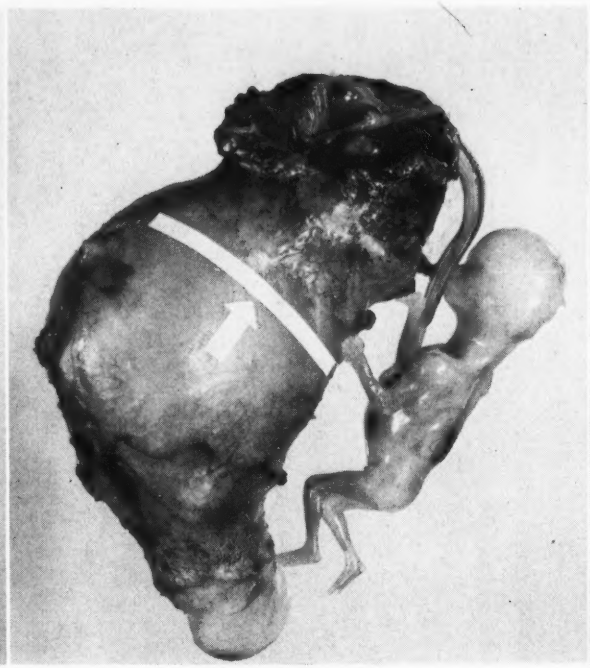

Fig. 2.

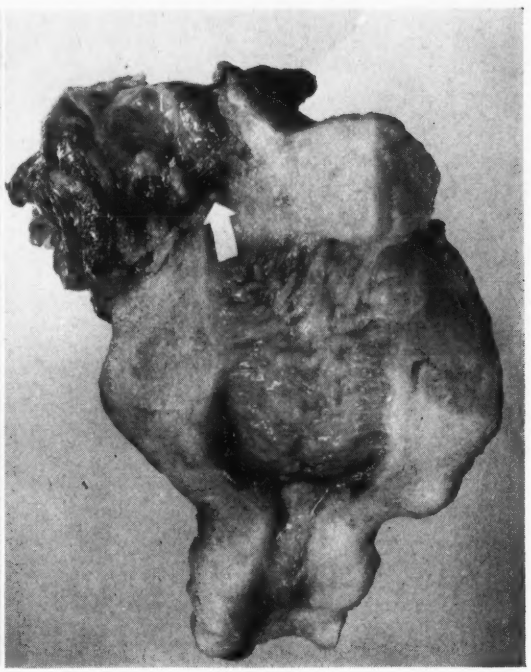

Fig. 3.

Fig. 1.—Interstitial gestation of 10 weeks' duration. Small perforation in cornu.

Fig. 2.—Same uterus, with gestation sac opened to expose placental attachment and fetus. White band indicates line of resection if repair were attempted.

Fig. 3.—Same uterus with uterine cavity exposed. Arrow indicates tubouterine junction and implantation site of placenta.

TABLE I. INCIDENCE OF INTERSTITIAL PREGNANCY, RACE, MORTALITY

HOSPITAL	NO. ECTOPIC PREGNANCIES	DEATHS	MORTALITY PERCENTAGE	NO. INTERSTIT. PREGNANCIES	PER CENT	RACE		DEATHS	MORTALITY PERCENTAGE
						WHITE	NEGRO		
Kings County	544	10	1.8	29	5.3	3	26	1	3.4
Jewish of Brooklyn	400	1	0.25	16	4.0	11	5	0	0
Combined Series	944	11	1.2	45	4.7	14	31	1	2.2

TABLE II. INCIDENCE OF INTERSTITIAL PREGNANCIES

AUTHOR	YEAR	TOTAL NO. ECTOPIC PREGNANCIES	TOTAL NO. INTERSTITIAL PREGNANCIES	PERCENTAGE
Von Rosenthal[6]	1896	1,324	40	3.0
Wynne[7]	1918	1,547	18	1.2
MacFarlane and Sparling[8]	1946	110	7	6.3
Dindia and Turcotte[9]	1946	90	1	1.1
Marchetti et al.[10]	1946	141	5	3.6
Frankel[11]	1948	356	8	2.2
Bell and Ingersoll[12]	1950	130	2	1.5
Present Series		944	45	4.7
Total		4,642	126	2.7

The interstitial portion of the Fallopian tube traverses the uterine musculature from the cornu to the upper angle of the uterine cavity, with which it communicates by a minute ostium. The rich vascular supply in this area of the uterus accounts for the frequent rapidity with which hemorrhage leads to shock after perforation.

Because of the myometrial hypertrophy accompanying pregnancy, an interstitial gestation may continue to develop for several weeks or months, and rarely to term. The duration of growth and its mode of termination are dependent upon the site of nidation in relation to the tubouterine ostium or the isthmial junction. There are three possible eventualities:

1. Rupture may occur, either into the peritoneal cavity or into the broad ligament. This is the most frequent outcome and usually takes place prior to the twelfth week of gestation (Table III). The greater the proximity of

TABLE III. DURATION OF PREGNANCY AT TIME OF RUPTURE IN 44 CASES*

WEEKS OF GESTATION (FROM LAST MENSTRUAL PERIOD)	NO. CASES
0- 4	5
5- 8	17†
9-12	13
13-16	7
17-20	1
21-24	0
25-28	1

*One case was accidentally found unruptured during laparotomy for the removal of a dermoid cyst of an ovary.

†In 5 cases there was no amenorrhea; duration of pregnancy estimated from size of the embryo found in the peritoneal cavity during laparotomy.

the original implantation to the isthmus, the earlier is rupture prone to occur. Occasionally the embryo may continue to develop at the secondary site as an abdominal pregnancy (Figs. 1, 2, and 3).

2. The gestation sac may be extruded into the upper angle of the uterine cavity, resulting usually in spontaneous abortion. Except for possible retention of placental tissue at the tubouterine junction, it is indistinguishable from any spontaneous abortion. However, the gestation may continue to term, and here, too, the placenta may be retained following parturition. This is the group designated "angular" pregnancy by Kerr and Anderson.

3. Rarely, the ovum may continue to develop within the substance of the uterus to term.[2, 13-15]

The etiology of ectopic pregnancy remains obscure. As noted by most authors, the most common predisposing factors are transmigration of the ovum, pelvic inflammatory disease, previous ectopic pregnancy, previous pelvic surgery, and sterility (Table IV). No evidence of any pre-existing disease or abnormality within the pelvis was noted in 24 of the 45 patients with interstitial pregnancy. In 5 cases where transmigration of the ovum was a predisposing cause, the homolateral adnexa had previously been removed.

TABLE IV. PREDISPOSING CAUSES IN 45 CASES

	NO. CASES	PERCENTAGE
Transmigration of the ovum	12	26.7
Pelvic inflammatory disease	10	22.2
Previous ectopic pregnancy	5	11.1
Previous laparotomy	5	11.1
Sterility	5	11.1
Induced abortion	2	4.4
Uterine fibroids	3	6.6
None	24	54.4

The majority of the patients were in the 25 to 35 year age group. The over 2 to 1 ratio of Negro women to white women in this series is compatible with Anderson's figures demonstrating about 50 per cent greater frequency of ectopic pregnancy in Negroes.[16] Three-fourths of the patients had borne one or more children; the remaining 11 patients had either never been pregnant or had pregnancies terminate in spontaneous abortions, thus confirming the impression that low fertility and infertility are commonly associated with ectopic pregnancy.[17]

TABLE V. RELATIVE DISTRIBUTION OF SIGNS AND SYMPTOMS

	NO. CASES		PERCENTAGE	
Abdominal pain only	5		11.1	
Abdominal pain and anomalous vaginal bleeding	5		11.1	
Abdominal pain and amenorrhea	17		37.8	
Abdominal pain, bleeding, and amenorrhea	18		40.0	
Shock		32		71.2
No shock		13		28.8
Total	45	45	100.0	100.0

The manifestations of an unruptured interstitial pregnancy are not characteristic. Often the patient is entirely symptomless, except perhaps for the usual subjective complaints of pregnancy; the first evidence of abnormality

may be an acute abdominal catastrophe. More often, however, one or more of the cardinal signs and symptoms appear first, but even then the diagnosis is difficult because of the absence of a palpable adnexal mass. The asymmetry of the uterus consequent to an abnormal implantation within the interstitial portion of the tube may resemble that of a normal intrauterine gestation, or one complicated by a myoma.

The most frequent signs and symptoms are abdominal pain, amenorrhea, abnormal vaginal bleeding, and shock (Table V).

Fig. 4.

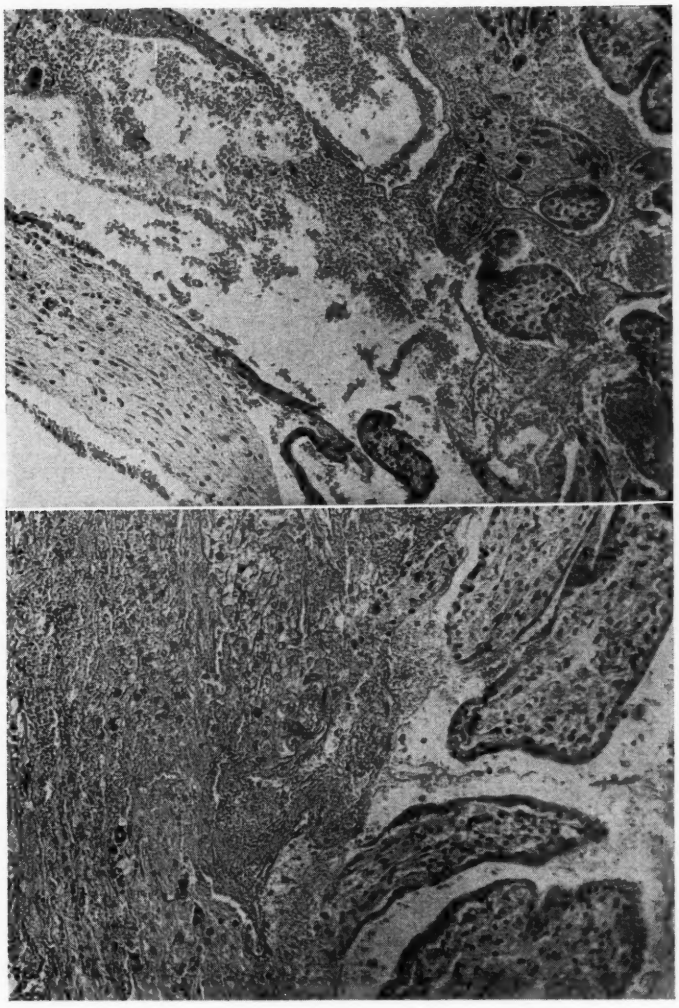

Fig. 5.

Fig. 4.—Uterine musculature adjacent to site of perforation. Note marked attenuation of the myometrium.

Fig. 5.—Section through placental site, distal to area of perforation. Note hemorrhagic infiltration and disruption of muscle fibers.

Pain.—Abdominal pain is present in all the cases. Insidiously mild and cramp-like at first, the recurrent pain becomes progressively more severe and reaches its peak of intensity when perforation occurs. Although the exact

cause of this pain prior to rupture is not clear, it is probably a result of both marked stretching and thinning of the surrounding myometrium, and hemorrhage into the uterine musculature as well as into the subplacental region, as noted in Figs. 4 and 5.

Palpation of the uterus often reveals an exquisite sensitivity in the immediate region of the irregular enlargement, a sign described by many others.[18, 19] No constant time relationship exists between the onset of pain and vaginal bleeding; the latter most often appears later by many weeks, or not at all.

Amenorrhea.—Only three-fourths of the patients gave a history of amenorrhea. No abnormality or variation of the menstrual cycle was noted by 10 of the 45 patients, and pregnancy had not been suspected. Amenorrhea in ectopic pregnancy has been reported as appearing in from 50 to 77 per cent of the patients.[8, 20]

Vaginal Bleeding.—Anomalous vaginal bleeding was the least common of all the signs and was noted by 51 per cent of the patients. When it did appear it was usually several days or weeks after the onset of abdominal pain. The oft-described triad of anomalous vaginal bleeding, pain, and amenorrhea was noted in only 18 of the 35 patients who were amenorrheic (Table V). The relative infrequency of anomalous bleeding in interstitial pregnancy as compared to the more common variety of extrauterine pregnancy can be explained by the persistent viability of the conceptus in this portion of the tube until rupture occurs. Death of the ovum takes place earlier in the other types of tubal gestation, so that the hormonal control of the decidua is disturbed and "spotting" appears in about 75 per cent of these patients.[4]

Shock.—Because the region is highly vascular, rupture through the cornu of the uterus most often results in massive intraperitoneal hemorrhage and rapid shock. Thirty-two, or 71.2 per cent, were in shock, either when admitted to the hospital or shortly thereafter. This is an incidence of peripheral vascular collapse from 2½ to 5 times greater than is reported for all other varieties of ectopic pregnancy.[12, 21, 22]

Accurate diagnosis of interstitial pregnancy is seldom made prior to laparotomy. The signs and symptoms after perforation are those of a ruptured tubal gestation, except that shock appears more rapidly and is more profound. Vaginal palpation of an asymmetric uterus with a tender cystic swelling at one or other cornu should lead to a suspicion of interstitial pregnancy, even before perforation has occurred. The significance of this finding is enhanced by associated abdominal pain and a history of amenorrhea. A previous pelvic examination that has revealed a uterus of normal size and contour, with normal adnexa, is of inestimable value in ruling out an acute degeneration of a fibroid or torsion of an ovarian cyst (Figs. 6 and 7).

An interstitial pregnancy may simulate a threatened or incomplete abortion. While the absence of chorionic villi in curettings does not of itself indicate ectopic pregnancy, the continued enlargement of a tender cystic mass in a cornu of the uterus is highly suggestive.

When the abdomen is opened, the relationship of the irregular uterine enlargement to the insertion of the round ligament is the key to the diagnosis.

In an interstitial pregnancy this cystic enlargement is superior to the point of insertion, and the other portions of the uterus are only slighly increased in size. In an intrauterine gestation the entire uterus is symmetrically enlarged, although some irregularity may be noted. An intraligamentous pregnancy is suggested when the round ligament courses over the anterior aspect of the mass. The rare case of interstitial gestation that reaches term is usually thought to be abdominal pregnancy or missed labor. The true diagnosis is eventually revealed when laparotomy is performed for either of these two conditions.

Fig. 6.

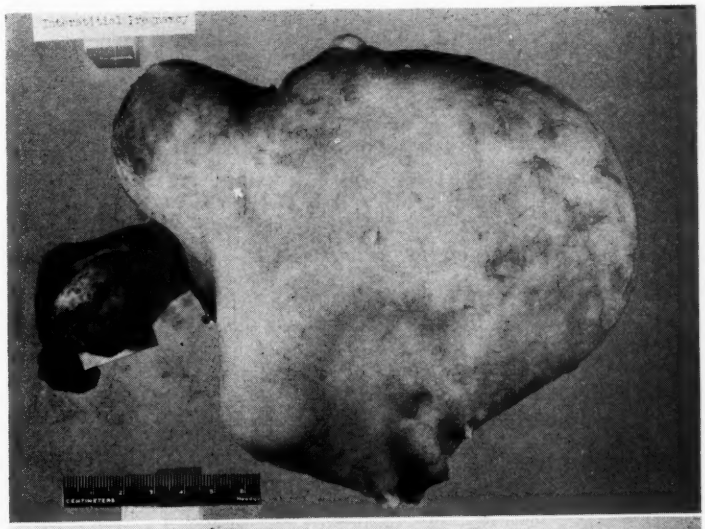

Fig. 7.

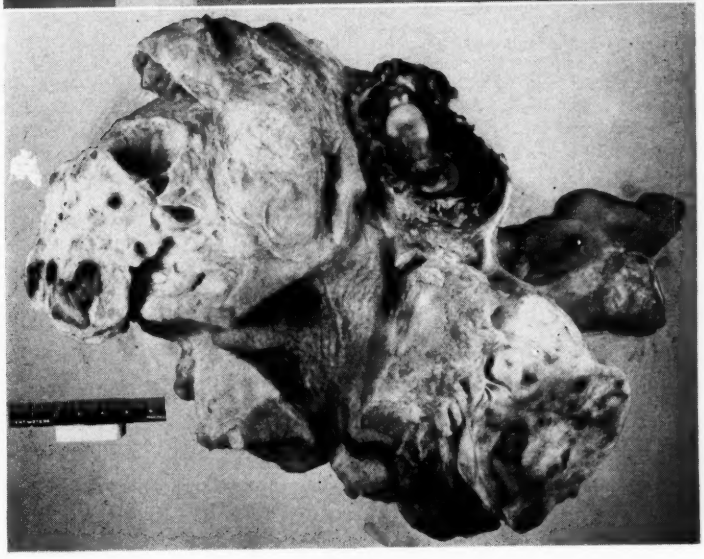

Fig. 6.—Uterus with 11 weeks' interstitial pregnancy in right horn, unruptured. A large myoma occupies the left cornual region. The attached right adnexa contain a corpus luteum of pregnancy.

Fig. 7.—Uterus laid open, revealing the pregnancy within the interstitial portion of the right tube. Marked necrobiosis and hemorrhage are present in the myoma.

Immediate surgery with simultaneous blood replacement in adequate amounts is the treatment for interstitial pregnancy. Despite the degree of shock that may accompany perforation, there should be no delay in the performance of surgery aimed at control of the source of bleeding, for only by arresting the hemorrhage will the patient be able to recover from shock. Intra-arterial transfusion in such cases may prove to be a lifesaving measure.

A laceration associated with rupture of an interstitial gestation of less than eight weeks' duration can often be repaired by wedge resection of the affected cornual area, similar to that performed with the usual salpingectomy. In the more advanced interstitial pregnancy the large area involved precludes resection, and hysterectomy is the indicated procedure (Fig. 2; Table VI). It can almost always be performed more quickly and hemostasis is attained earlier than in resection with repair. The latter is a time-consuming procedure, equivalent to a partial fundectomy, and is associated with increased blood loss because of the extreme vascularity and friability of the tissues. Since control of the hemorrhage is delayed until the operation nears completion, attempt at repair is fraught with grave hazard for the patient. The sole fatality in this series occurred in the operating room, following a futile attempt to preserve the uterus by cornual resection, despite a rather large perforation in a deeply shocked patient. Resort to hysterectomy in a final desperate attempt to control the bleeding was too late. Only with a patient in good condition is an extensive resection ever justified. The principles of treatment are similar to those of a ruptured gravid uterus.

TABLE VI. TREATMENT

OPERATION	NO. OF CASES		PERCENTAGE
Hysterectomy		18	40.0
Repair of perforation		27	60.0
Wedge resection of uterine cornu	22		
Partial fundectomy	5		
Total		45	100.0

Prompt hospitalization, immediate surgery, and adequate blood transfusion have reduced the high mortality formerly associated with this grave condition. The single death in this series represents a mortality rate of 2.2 per cent, which is still considerably higher than the 1.2 per cent for the 944 ectopic pregnancies of all varieties. While the reduction in the death rate can be attributable to modern therapy, an occasional massive hemorrhage may be so rapid that death supervenes before treatment can be instituted.

The scar left by cornual resection may play an important role in future childbearing. The larger the resection, the more is the scar comparable to that of a classical cesarean section or extensive myomectomy. It has been demonstrated that the latter types of scar are prone to rupture during pregnancy and labor, so that patients who have had extensive cornual resections should be delivered preferably by elective cesarean section.[23] If vaginal delivery is the method selected, then postpartum exploration of the uterine cavity is indicated for possible rupture. The smaller wedge resections are far less hazardous in regard to future vaginal delivery, since only two such cases have been reported as subsequently ruptured.[24, 25]

Summary

1. An analysis of 45 cases of interstitial pregnancy has been presented. These were obtained from a total group of 944 ectopic pregnancies of all varieties, an incidence of 4.7 per cent.

2. There was one death, a mortality rate for interstitial pregnancy of 2.2 per cent.

3. Perforation occurred most frequently between the fifth and twelfth weeks of gestation, contrary to the general impression of late rupture.

4. Transmigration of the ovum was noted in 26.7 per cent of the cases.

5. The most frequent complaint was abdominal pain. Amenorrhea, anomalous vaginal bleeding, and shock were other important signs and symptoms.

6. Profound shock appeared in 71.2 per cent of the patients with cornual perforation. This was the result of massive intraperitoneal hemorrhage.

7. The diagnosis of interstitial pregnancy is seldom made prior to rupture. Tender cystic enlargement at one horn of the uterus is suggestive of this type of ectopic gestation.

8. During laparotomy an interstitial pregnancy may be recognized by asymmetric enlargement of the uterus superior to the insertion of the round ligament, without a corresponding enlargement of the rest of the organ.

9. Treatment is immediate surgery and blood transfusion. Because of the greater speed with which it usually can be accomplished, and because control of hemorrhage is almost immediate, hysterectomy is preferable to cornual resection of an extensive laceration.

References

1. Thunig, L. A.: Am. J. Obst. & Gynec. **48**: 114, 1944.
2. Grusetz, M. W., and Polayes, S. H.: Am. J. Obst. & Gynec. **48**: 379, 1944.
3. Delascio, D., and Assali, N. S.: An. brasil. de ginec. **18**: 238, 1944.
4. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., p. 519.
5. Kerr, J. M. M., and Anderson, A. F.: Brit. J. **1**: 1113, 1934.
6. Von Rosenthal, J. Centralbl. f. Gynäk. **20**: 1297, 1896.
7. Wynne, H. M. N.: Bull. Johns Hopkins Hosp. **29**: 29, 1918.
8. MacFarlane, K. T., and Sparling, D. W.: Am. J. Obst. & Gynec. **51**: 343, 1946.
9. Dindia, A. H., and Turcotte, V. J.: Am. J. Obst. & Gynec. **52**: 321, 1946.
10. Marchetti, A. A., Kuder, K., and Kuder, A. A.: Am. J. Obst. & Gynec. **52**: 544, 1946.
11. Frankel, A. N.: Am. J. Obst. & Gynec. **56**: 574, 1948.
12. Bell, J. W., and Ingersoll, F. M.: Am. J. Obst. & Gynec. **60**: 174, 1950.
13. Hull, E. T.: Am. J. Obst. & Gynec. **28**: 452, 1934.
14. Stapleton, G.: Brit. M. J. **1**: 879, 1935.
15. Ishizu, S., and Fujii, Y.: Cited by Grusetz and Polayes.[2]
16. Anderson, G. W.: Am. J. Obst. & Gynec. **61**: 312, 1951.
17. Grant, A.: Fertil. & Steril. **2**: 302, 1951.
18. Johnston, L. W., and Moir, J. C.: J. Obst. & Gynaec. Brit. Emp. **59**: 85, 1952.
19. Blaikley, J. B.: Proc. Roy. Soc. Med. **29**: 1648, 1935.
20. Henderson, D. N., and Bean, J. L.: Am. J. Obst. & Gynec. **59**: 1225, 1950.
21. Beacham, W. D., Collins, C. G., Thomas, E. P., and Beacham, D. W.: J. A. M. A. **136**: 365, 1948.
22. Draa, C. C., and Baum, H. C.: Am. J. Obst. & Gynec. **61**: 300, 1951.
23. Pedowitz, P., and Felmus, L. B.: Obst. & Gynec. Surv. **7**: 305, 1952.
24. Schenck, S. B., and Rader, M. J.: Am. J. Surg. **52**: 494, 1941.
25. Pleuger, R.: Zentralbl. f. Gynäk. **71**: 1095, 1949.

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PELVIC TUBERCULOSIS AND PREGNANCY

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GENITAL tuberculosis is considered by most gynecologists to be a cause of complete and incurable sterility. It has become evident that "latent" tuberculosis, asymptomatic except for sterility, is perhaps ten times more common than "active" genital tuberculosis, mainly as a result of the increasing use of endometrial biopsy, cultures of the menstrual blood, and hysterosalpingography. Cross[3] states, "In spite of what anybody says there has never been a case of pregnany recorded in a patient whose endometrium has proved to be tuberculous." Tuberculosis in the female pelvic organs is a known factor in infertility. However, this localized disease may not disturb the patency of the tubes as proved by insufflation and hysterosalpingograms. Cases of tubal pregnancy have been reported occurring in tuberculous Fallopian tubes (Jameson[1a]). When the physiology of gestation is not impaired by the disease these patients may at times become pregnant.

Halbrecht[2] records that of 71 women with latent genital tuberculosis discovered by biopsy or culture none became pregnant during observation and many had been sterile for almost 20 years. Sharman[4] has shown that of 122 patients with endometrial tuberculosis, only 1 patient became pregnant and she after 17 years of marriage.

Viewed somewhat differently, the incidence of previous pregnancy in married women with known genital tuberculosis is of interest. According to Greenberg,[5] this percentage is 36.5 per cent, whereas according to Held[6] it is about 40 per cent, and Smith[7] states it to be 35.2 per cent. Jedberg[8] found that 13 per cent of 186 women with genital tuberculosis had borne children, and in all instances before the clinical onset of the disease. However, it should be noted that 2 patients had delivered only 4 and 10 months, respectively, before the diagnosis of genital tuberculosis was made.

A survey of the literature does show that pregnancy and genital tuberculosis may be associated, however rare this occurrence may be. Runge[9] described an autopsied fatal case of abortion with pulmonary, genital, and placental tuberculosis. Weil[10] reported 2 fatal autopsied cases of abortion and genital tuberculosis in women who died of miliary tuberculosis shortly after abortion. Mensing[11] described a case in which a histological diagnosis was made after curettage of pregnancy and tuberculous endometritis. Six months following intrauterine radium the patient became pregnant, and was delivered at full term. Holtz[12] reported 2 cases of adnexal tuberculosis and pregnancy terminating in the sixth month by abortion and followed by miliary tuberculosis.

Ericksen[13] cites 2 patients with tuberculous salpingitis who had normal deliveries. Roulland[14] reported 2 similar cases. Jedberg[8] cited a patient who became pregnant in spite of recent tuberculous endometritis. Abortion in the third month was followed by curettage and the development of tuberculous salpingitis and miliary tuberculosis. Russell[15] reported a similar case.

Sutherland[16a] found that in 6 of 60 patients with genital tuberculosis, the tuberculous lesion developed during pregnancy or in the postpartum period. Similar cases of Daniels, Jameson, Georgescu and associates and Henig and King are cited. In 5 of the 6 cases the human tubercle bacillus was isolated. Hurter[16b] described the postpartum development of pelvic tuberculosis 10 days after a premature spontaneous delivery.

Stallworthy[17] reported 1 case of pregnancy in 78 cases of genital tuberculosis. In the discussion of his paper, Ten Berge[18] stated that "infection after delivery or abortion which does not respond to penicillin must lead to suspicion of tuberculosis which proved well founded in 2 of our patients," and Snaith[19] cited a patient in whom pulmonary tuberculosis was diagnosed in the sixteenth week of pregnancy. Premature delivery at the twenty-ninth week was followed in the eighth postpartum week by an adnexal mass and tuberculosis of the endometrium and cervix on biopsy. Sharman's[4] case has already been cited but the termination of pregnancy was not stated.

A contrast to these views on the rarity of the association of genital tuberculosis and pregnancy is found in the papers of Fruhinsholtz and his coworkers[20, 21] Sixty such cases have been collected by him, including 6 cases of genital tuberculosis treated by conservative surgical methods in which subsequently conception and normal delivery occurred without complication. They stated that pregnancy and genital tuberculosis are not rare and believe that pregnancy is frequently interrupted by abortion. Although these patients may show no symptoms prior to the pregnancy, pelvic tuberculosis manifests itself at the time of abortion or delivery, probably because of the trauma involved by parturition. The immediate postabortal or puerperal period is most dangerous because the uterus is exposed to secondary infection at this time. Acute tuberculous peritonitis and miliary tuberculosis commonly occur.

The role that streptomycin and other antituberculous drugs will play in the relief of infertility of patients with pelvic tuberculosis cannot be clearly assessed at this time. Wood and Elqueta[22] conclude that the drug does not cure sterility. Schockaert[23] reports only one pregnancy after treatment. Bedrine and Houline[24] observed 2 pregnancies in 15 women after treatment but one ended in abortion and one was an ectopic pregnancy. Rabau[25] reported a case of pregnancy following the healing by streptomycin of endometrial tuberculosis proved by bacterial culture. Abortion occurred in the third month, but, according to the author, "it seems unlikely that it was caused by Koch's bacillus." It should be noted that 42 cases of tuberculous salpingitis and ectopic pregnancy have been collected by Kistner and associates.[26]

Case Report

D. A., No. 52-2402, a 19-year-old Negro woman, gravida i, para 0, was admitted to the Gynecological Service of Harlem Hospital on Feb. 6, 1952, complaining of amenorrhea for 3 months followed by abdominal pain and vaginal bleeding of 48 hours' duration. Her last menstrual period had been in November, 1951. Menstruation began at 16 years of age, occurred every 28 days, and lasted 2 days. The past history was essentially negative. Tuberculosis, venereal diseases, pelvic inflammatory disease, and attempts to induce abortion were denied. A fetus and placenta were passed spontaneously on the day of admission.

Fig. 1.

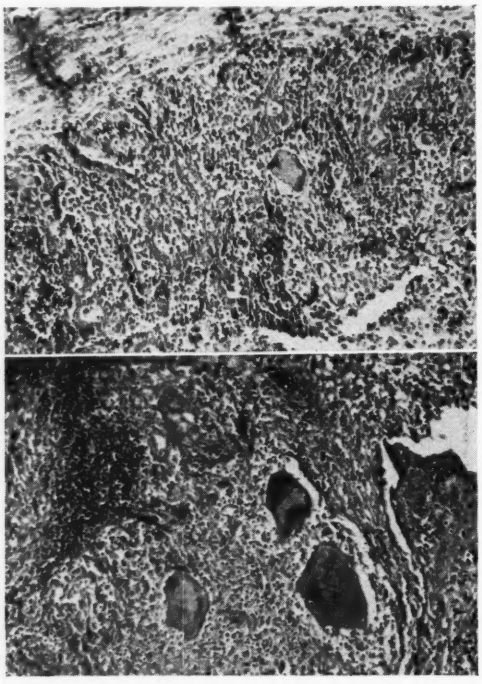

Fig. 2.

Fig. 1.—Tuberculosis of the Fallopian tube.
Fig. 2.—Tuberculosis of the ovary.

Physical examination revealed a well-developed, well-nourished woman in no acute distress. The blood pressure was 118/70, pulse 110, and temperature 98.6° F. The abdomen was flat and tender; there were no palpable masses. Pelvic examination revealed normal external genitals. The introitus was normal. The uterus was enlarged to the size of a 7 weeks' gestation. No masses or tenderness were noted in the fornices and cul-de-sac. The cervix was open, and on speculum examination blood clots and membranes were seen protruding from it. The urine was negative; sedimentation rate, normal; blood counts not unusual; Kahn test negative. A diagnosis was made of infected incomplete abortion. The temperature gradually rose to 104° F. in spite of massive doses of penicillin, aureomycin, and intravenous fluids. It was believed that retained secundines accounted for the fever, and on Feb. 13, 1952, on the seventh hospital day, dilatation and curettage were done. The pathological report was degenerated placental tissue.

After dilatation and curettage the patient's temperature remained at 103 to 104° despite penicillin and aureomycin therapy. Chest x-rays were reported as negative. Blood culture was sterile; on cervical culture beta hemolytic streptococci were isolated. The

sedimentation rate continued normal. The patient appeared acutely ill. Pelvic examination at this time revealed bilateral fixed tender masses in the fornices, extending into the cul-de-sac, the right larger than the left. A diagnosis of left postabortal pyosalpingitis and right tubo-varian abscess was made. Since there had been no response to aureomycin the patient was given 1 Gm. of streptomycin per day. After three days of streptomycin the temperature began to fall, and after six days it was normal. Because of the persistence of the adnexal masses, a laparotomy was performed on March 21, 1952, the forty-fourth hospital day.

On opening the peritoneum, marked adhesions between the omentum, pelvic viscera, and bowel were encountered. The omentum was extremely thick and friable. The uterus was of normal size and covered with grayish fibrinous material. The right tube was converted into a large pyosalpinx which ruptured during its mobilization, exuding thick greenish odorless pus. The right ovary was covered with grayish fibrinous material. The left tube was converted into a small pyosalpinx and the left ovary appeared normal. A right salpingo-oophorectomy and a left cornual resection were performed.

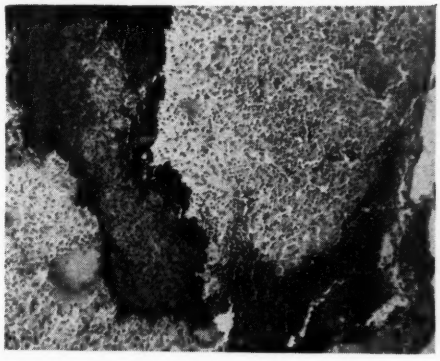

Fig. 3.—Tuberculosis of the endometrium as shown in the curettings.

The patient's postoperative course was uneventful. The temperature remained normal until discharge. The pathological report of the operative specimen was tuberculous salpingo-oophoritis (Figs. 1 and 2). The patient was placed on 14 Gm. of para-amino-salicylic acid per day along with streptomycin. Catheterized urine was reported as negative for tuberculosis on guinea pig inoculation. An endometrial biopsy was done on March 31, 1952, ten days postoperatively. The pathological report was tuberculous granulation tissue (Fig. 3). The patient was discharged in good condition to the clinic on March 31, 1952. Examination 10 months later showed her to be free of symptoms and in excellent general health. The pelvis was essentially negative and all therapy had been discontinued.

A case of pregnancy complicating genital tuberculosis is reported. This case terminated in an abortion; salpingo-oophoritis developed and was treated with conservative surgery.

We must assume that the tubes were open in order that the patient could become pregnant At laparotomy both tubes were closed. This must have happened after conception occurred. The patient probably had a tuberculous endometritis and possibly a tuberculous endosalpingitis. The development of masses postabortally would signify a flare-up of the quiescent condition and progression to the pathology found at operation.

Comment

The coexistence of pelvic tuberculosis and intrauterine pregnancy, while rare, has been shown to occur. Most observers believe that pre-existing pelvic tuberculosis prevents pregnancy and that genital tuberculosis occurring in these patients is secondary to the trauma of abortion and parturition. On the other hand, there are a number of apparently authentic cases which prove

that genital tuberculosis preceded pregnancy and that pregnancy may activate latent tuberculosis. There are many factors which make it difficult to prove which of these viewpoints is correct, or even, possibly, whether both may not be correct in different patients. The protean nature of tuberculous disease may lead to great difficulties in clinical diagnosis. The histological vertification of tuberculosis is at times quite difficult; many agents such as Lipiodol can produce a granulomatous lesion which can trap the unwary observer into a false diagnosis of tuberculosis. Until recently the bacteriological confirmation of tuberculosis was difficult. In any event the majority of cases of pelvic tuberculosis associated with pregnancy become manifest after delivery or abortion as in the case reported here.

Why does pregnancy occur with such rarity in cases of genital tuberculosis? It is generally agreed that endometrial tuberculosis is invariably secondary to and associated with tubal tuberculosis. If the tubes are not patent the cause of sterility is obvious. However, tubal occlusion does not always occur. Thus, Sharman found the tubes occluded in 66.9 per cent of patients with known endometrial tuberculosis. Rabau[28] found this figure to be 75 per cent and Stallworthy[17] thought it was 50 per cent. Therefore occluded tubes cannot be the only cause for infertility. The possibility exists that even though these diseased tubes are not closed their function is impaired. Surprisingly, there are records of 11 cases of tubal tuberculosis discovered at laparotomy and treated by conservative surgery in patients who subsequently delivered normal children. Fruhinsholz and associates mention 2 of their own cases and those of Oliver, Macnaughton-Jones, Tedenat, Muret, and Heully. Ericksen[13] and Roulland[14] have also reported similar cases. Delore and Chalier[29] stated in 1920 that they did not know one single case of genital tuberculosis followed by pregnancy, but in 1938 Chalier[30] reported a case of full-term pregnancy following linear salpingostomy for tubal tuberculosis (which illustrates the difficulty of dogmatic statements concerning genital tuberculosis).

What role does the endometrium play in the production of infertility in such cases? Although little work has been done on this question it would seem surprising if the degenerated endometrium could provide a suitable nidation for a fertilized ovum.

From the clinical point of view the nature of tuberculous disease occurring after abortion or delivery has apparently undergone change. In the older references an acute onset usually fatal and associated with miliary tuberculosis is frequent. Today, the onset is usually insidious but should be suspected by the persistence of fever and the formation of adnexal masses resistant to the usual antibiotic therapy. Unfortunately, the diagnosis is often not made until operation or even later, so that conservative measures cannot longer be utilized. If tuberculosis is suspected, endometrial biopsy and culture may confirm the diagnosis and permit conservative therapy with streptomycin, para-aminosalicylic acid, or the newer antituberculosis drugs. Hysterography[31] is of value in the diagnosis of pelvic tuberculosis; in acute cases, however, the danger of severe exacerbation does not permit its use.

The prognosis in such cases does not seem worse than in genital tuberculosis uncomplicated by pregnancy in the light of present therapy.

Conclusions

1. A case of pregnancy terminating in abortion in the third month, in which tuberculous salpingo-oophoritis developed after abortion, is presented.

2. Pregnancy and genital tuberculosis occur rarely. The pertinent literature is summarized.

3. Tuberculous endometritis and salpingitis usually become manifest in the postabortal or postpartum period. Whether latent tuberculosis was present and activated or whether the infection is initiated after the trauma of abortion or parturition cannot be answered in the present stage of our knowledge. Women known to have pre-existing pelvic tuberculosis have the ability, although rarely, to become normally pregnant.

4. The infertility factor of genital tuberculosis is discussed.

5. Pelvic tuberculosis after abortion or delivery should be suspected by the persistence of fever and the concomitant appearance of adnexal masses resistant to the usual antibiotic therapy; such cases should have endometrial biopsy and culture of vaginal and uterine secretions. A trial of therapy with streptomycin and para-aminosalicylic acid may be of value.

References

1. Rabau, E., Hennon, J., and Casper, J.: Gynaecologia **127**: 248, 1949.
1a. Jameson, Edwin M.: Gynecological and Obstetrical Tuberculosis, Philadelphia, 1935, Lea & Febiger.
2. Halbrecht, I.: Tr. Internat. & Fourth Am. Congress on Obst. & Gynec. (supp. vol. Am. J. Obst. & Gynec.) **61A**: 250, 1951.
3. Cross, R. G.: J. Obst. & Gynaec. Brit. Emp. **59**: 742, 1952.
4. Sharman, A.: Fertil. & Steril. **3**: 144, 1952.
5. Greenberg, J. P.: Bull. Johns Hopkins Hosp. **32**: 52, 1921.
6. Held, E.: Gynaecologia **125**: 236, 1948.
7. Smith, G. van S.: Am. J. Obst. & Gynec. **16**: 701, 1928.
8. Jedberg, H.: Acta obst. et gynec. Scandinav. (supp. 1) **31**: 1, 1950.
9. Runge, E.: Arch. f. Gynäk. **68**: 388, 1903.
10. Weil, F.: München. med. Wchnschr. **57**: No. 7, p. 359, 1910.
11. Mensing, K.: Zentralbl. f. Gynäk. **60**: 1210, 1936.
12. Holtz, F.: Nord. Med. **8**: 2164, 1940.
13. Ericksen, B.: Acta obst. et gynaec. Scandinav. **27**: 249, 1947.
14. Roulland, M. H.: Compt. rend. Soc. franç. gynéc. **17**: 145, 1947.
15. Russell, P. M. G., Jackson, M. H., and Midgeley, R. L.: J. Obst. & Gynaec. Brit. Emp. **58**: 712, 1951.
16a. Sutherland, A. M., and Gamey, M. M.: Proc. Roy. Soc. Soc. Med. **45**: 411, 1952.
16b. Hurter, Lois: Proc. Roy. Soc. Med. **45**: 413, 1952.
17. Stallworthy, J.: J. Obst. & Gynaec. Brit. Emp. **59**: 729, 1952.
18. Ten Berge, B. S.: J. Obst. & Gynaec. Brit. Emp. **59**: 736, 1952.
19. Snaith, Linton: J. Obst. & Gynaec. Brit. Emp. **59**: 745, 1952.
20. Fruhinsholtz, A., and Feuillade: Gynéc. et obst. **10**: 305, 1924.
21. Fruhinsholtz, A., Richon, J., and Custelain: Gynéc. et obst. **41**: 241, 1941.
22. Wood and Elqueta: Bol. Soc. chilena de obst. y ginec. **16**: 30, 1951.
23. Schockaert, J. A.: Bull. Soc. belge de gynéc. et d'obst. **4**: 283, 1952.
24. Bedrine and Houline: Bull. Soc. belge de gynéc. et d'obst. **4**: 280, 1952.
25. Rabau, E.: J. Obst. & Gynaec. Brit. Emp. **59**: 743, 1952.
26. Kistner, R. W., Hertig, A. T., and Rock, John: Am. J. Obst. & Gynec. **62**: 1157, 1951.
27. Falk, H. C.: Editorial, Am. J. Surg. **81**: 595, 1951.
28. Rabau, E.: Fertil. & Steril. **1**: 517, 1950.
29. Delore, X., et Chalier, A.: La tuberculose génitale chez l'homme et chez la femme, Paris, 1920, O. Doin, p. 293.
30. Chalier, A.: Rev. franç. de gynéc. et d'obst. **33**: 577, 1938.
31. Rozin, S. J.: J. Obst. & Gynaec. Brit. Emp. **59**: 59, 1952.

IMPERFORATE ANUS COMPLICATING PREGNANCY

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IMPERFORATE anus is a congenital anomaly with a reported incidence by various authors of 1:1,500 to 1:5,000. Only one case was found in the modern literature where a Type III imperforate anus was complicated by a gravid uterus. The case reported here is presented not so much for its rarity but more for a demonstration of the adaptability of the organism to certain deviations from normal anatomy.

Imperforate anus was recognized and described in the third century A.D. but at that time it was regarded as an incurable monstrosity. The first surgical intervention for the condition is accredited to Paulus of Aegina in the seventh century. He advocated the blind plunge of a knife into the perineum in the hope of entering the rectal pouch. It was not until 1835 that Amusset recommended perineoplasty with mobilization of the rectal pouch. Velpeau in 1844 advocated sigmoid colostomy following unsuccessful perineal dissection. As early as 1894 Delageniere suggested the use of combined abdominoperineal anaplasty, but it was not until 1948 that this procedure was revived by Rhoades and co-workers.[1] In 1942 Harken[2] called attention to the gravity of the imperforate anus problem by pointing out the high incidence of nonsurgical mortality. Mayo and Rice[3] stated in 1950: "We feel that our goal is primarily a satisfactory method of defecation and urination with control and separation of the urine and feces. Anatomic correction of the malformation is of secondary importance." Recent authors are in favor of anatomical restoration (Moore and Lawrence[4] and Santulli[8]) so that at present the emphasis is on specific evaluation and treatment on an individual basis. Santulli[8] believes that all patients with fistulas should be given the benefit of definitive surgery, regardless of age, since no optimal age limit for surgical intervention has been established.

In 1934 Ladd and Gross[7] published a classification of this anomaly, which has since become generally accepted. The anomaly is classified into four types, as follows:

Type I.—Stenosis at the anus or lower rectum which is due to incomplete rupture of the anal membrane. This is an unusual form of the anomaly in most of the series reported.

Type II.—The membranous form of imperforate anus, which is due to a persistence of the anal membrane. This type is also unusual.

Type III.—The anus is imperforate and the rectum ends as a blind pouch a variable distance from the perineum. This is the most common type, accounting for 70 to 80 per cent of the reported cases.

Type IV.—The anal canal and lower rectum form a pouch which is separated for a variable distance from the blind rectal pouch. This is the most unusual form of the anomaly.

It is now generally agreed that the condition is more frequent in the male, a ratio of 2:1 being cited by some authors. It is also accepted that fistulas are most frequently associated with Type III. Santulli[3] has reported in his series of 62 patients an incidence of 93 per cent of fistulas occurring in the females with Type III. Norris and Brophy[5] state that rectourinary and rectouterine fistulas are very uncommon in the female. High rectovaginal fistula does occur, although most of the fistulous tracts open in the lower third of the vagina or into the vulva immediately anterior to the fourchette. Moore and Lawrence[4] state that patients with adequate fistulous decompression are not often referred to the hospital during the first hours or days of life. Patients with vaginal or perineal fistulas may occasionally go for months or even years without serious difficulties.

Attention has been called to the "Imperforate Anus Syndrome" by Moore and Lawrence.[6] This syndrome is characterized by the high incidence of associated abnormalities occurring in the genitourinary system, the vertebral-neurological system, the gastrointestinal system, the cardiovascular system, the female genital system, or the abdominal wall and the extremities.

Moore and Lawrence mentioned a 19-year-old patient who was delivered by cesarean section of a 9 pound baby. Prior to delivery the patient had had an unsuccessful perineal anaplasty with recurrence of vaginal fistulas. To our knowledge, this is the second such case to be reported.

Case Report

M. B., No. 327517, was a 21-year-old primigravida who was born in Tennessee, migrated to Cleveland at 19½ years of age, and had worked as a hospital ward aide for 10 months.

As a child she suffered from fecal incontinence and protracted constipation for which she was treated with laxatives. Her stools were pencil sized and she observed that they were smaller than those of her companions. Although her mother noted that her "anal orifice" was smaller than usual, no medical opinion was sought. Her stools were of normal color, and she denies blood or pus in the feces. No attention was paid to diet and she had never developed symptoms of intestinal obstruction. There was no history of genitourinary symptoms or cardiovascular distress.

Catamenia occurred at the age of 15, was of normal periodicity and flow, but was associated with dysmenorrhea. At this age the patient was continent of feces, but had bowel movements every 7 to 10 days, despite ingestion of varied amounts of the purgatives in vogue.

Four years ago she developed perirectal abscess, and was hospitalized for six weeks. Prior to hospitalization she had been discharging feces from a single opening, but after drainage of the abscess she developed numerous fistulas which were constantly draining feces, pus, and small amounts of blood. She was told that her anus was too small, and that an operation was necessary. However, operation was postponed because of poor nutritional status and anemia which failed to respond satisfactorily despite multiple whole blood transfusions. She was discharged on bed rest without further surgery. The next nine months were spent in bed, during which period she was amenorrheic and incontinent of feces. At the end of this time, a normal menstrual pattern was re-established and she regained bowel control.

She was first seen in the gynecologic clinic of this hospital nine months ago with complaints of a missed period and discharge. She was found to have an imperforate anus with multiple rectovaginal and perineal fistulas. Pregnancy was confirmed and she was followed in the prenatal clinic. Abdominal delivery was planned but one week from term she developed partial abruptio placentae and was delivered of a live 6 pound, 10 ounce infant by low cervical cesarean section.

On admission the vital signs were normal. The patient appeared as a well-developed, well-nourished Negro woman in early labor. There was a Grade I precordial systolic murmur heard best over the pulmonic area. There were two small fistulas in the lower third of the vagina which contained small amounts of soft feces. There were multiple fistulas in the perineum, some closed, and others patent. The largest fistula admitted a finger and was epithelized (Fig. 1).

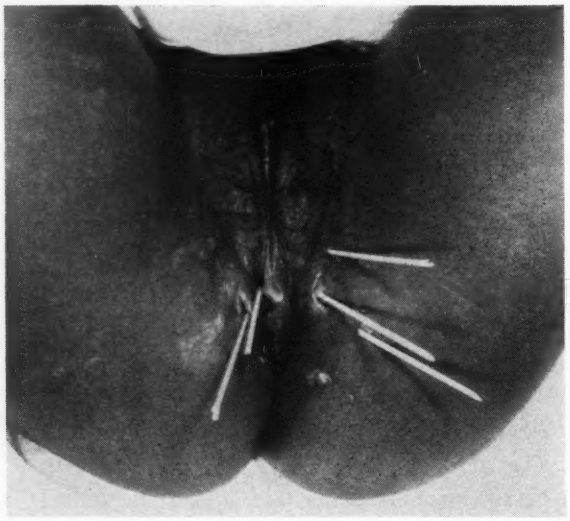

Fig. 1.—Patient with imperforate anus and multiple rectovaginal and rectoperineal fistulas.

The urine was normal. Cystoscopy, intravenous pyelography, and roentgenograms of the chest and lumbar spines showed no abnormality. The hematocrit was 34 per cent and the hemoglobin concentration was 10.5 Gm. per cent. She received 500 c.c. whole blood after cesarean section. Her postpartum course was uneventful and two weeks later she was transferred to the General Surgical Service for definitive therapy for her congenital anomaly.

Transverse colostomy was performed in the fourth postpartum week. Her postoperative course was uneventful and she was discharged, to be readmitted at a later date for abdominoperineal anaplasty.

Comment

Despite her abnormal anatomy this patient had reached the childbearing age without serious difficulty. Surgical correction was undertaken because these patients usually develop recurrent bouts of perianal abscesses. Some patients require emergency surgery; others, as the patient here reported, adjust remarkably well by substituting for the anal orifice and sphincter fistula and employment of buttock muscles.

When this patient was first seen the uterus was gravid and the vagina contained feces. That the patient should become pregnant under such adverse circumstances would tend to imply that not all bacteria affect the sperm adversely.

References

1. Rhoades, J. E., Pipes, R. L., and Randall, J. P.: Ann. Surg. **127**: 552, 1948.
2. Harken, D. E.: Surgery **11**: 422, 1942.
3. Mayo, C. W., and Rice, R. A.: Surgery **27**: 485, 1950.
4. Moore, T. C., and Lawrence, E. A.: Surgery **32**: 352, 1952.
5. Norris, W. J., Brophy, T. W., and Brayton, D.: Surg., Gynec. & Obst. **95**: 257, 1952.
6. Moore, T. C., and Lawrence, E. A.: Surg., Gynec. & Obst. **95**: 257, 1952.
7. Ladd, W. E., and Gross, R. E.: Am. J. Surg. **23**: 167, 1934.
8. Santulli, T. V.: Surg., Gynec. & Obst. **95**: 601, 1952.

THE BARTON OBSTETRIC FORCEPS: A HISTORY

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TWENTY-NINE years ago this year the Barton obstetric forceps was used for the first time on a living patient. Since that date this unique and controversial instrument has run the gamut of popularity. It enjoyed considerable prominence for some years as an extremely useful adjunct in the management of arrested transverse positions of the occiput—the exact situation for which it was designed. The limitations of the forceps were discovered by experience and it has now probably assumed its fairly limited but useful position in the forceps arsenal of the obstetrician.

This instrument is one of the few well-known forceps of strictly American origin and design. The chronology of its development is of some interest and is a good example of the multiple processes of modification through which an original instrument must go to eliminate its faults.

The developmental history of the Barton forceps and biographical notes of its originator, Dr. Lyman G. Barton, have been rather completely presented in a book entitled *The Barton Forceps,* compiled by F. C. Dossert and published in 1949. Unfortunately, this was a privately printed limited edition and many obstetrical practitioners have never had the opportunity of becoming acquainted with this interesting story. It is justifiable, therefore, to record again the history of the Barton forceps and to add certain additional data recently discovered in the records of the Sloane Hospital for Women.

The concept of an obstetrical forceps for anteroposterior application is not a new one and a number of such instruments have been devised. The first such forceps was described in 1805 by Uytterhoven, Chief Surgeon of St. John's Hospital in Brussels, Belgium. The blades of this instrument were designed to be applied, one against the promontory of the sacrum, and the other against the symphysis pubis. Poullet[1] said of this forceps, "No one seems to have used the instrument on the living. The construction of the instrument is based purely on theory. The instrument represents a useful idea, if it could be applied: the compression of the head by the forceps only in the antero-posterior direction, coincident with compression exerted in the pelvis."

In 1849 M. Baumers[4, 19] of Lyons, France "reinvented" Uytterhoven's forceps, apparently not being aware of the latter's attempt 44 years earlier. This was a long forceps without pelvic curve and it had essentially straight shanks. The blades formed an angle of about 135 degrees with the horizontal as does Barton's instrument. There was, however, no movable joint for the

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anterior blade. In 1878 Dr. W. L. Reid[2] of Glasgow, Scotland, introduced a forceps for anteroposterior application whose chief peculiarity, in addition to its proposed method of application, was a marked perineal curve. Dr. Henry D. Fry[6] of Washington, D. C., who became Professor of Obstetrics at Georgetown University in 1890, showed an instrument in 1889 which he designed for application to the biparietal "before forward rotation of the occiput has taken place." Its chief feature was a long posterior blade which combined a pelvic and cephalic curve. The anterior blade was shorter with similar curves and had a fixed angle between the blade and the shank. A traction bar was included in the design. Dr. Samuel Sloan[5] of Glasgow, Scotland, also described in 1889 an anteroposterior forceps for cephalic application when the head was transverse and failed to enter the pelvic brim. This instrument was described as "first a compressor and then a tractor." Interestingly enough, Sloan recommended applying the anterior blade of this forceps by introducing the blade laterally and "wandering" it into position under the symphysis.

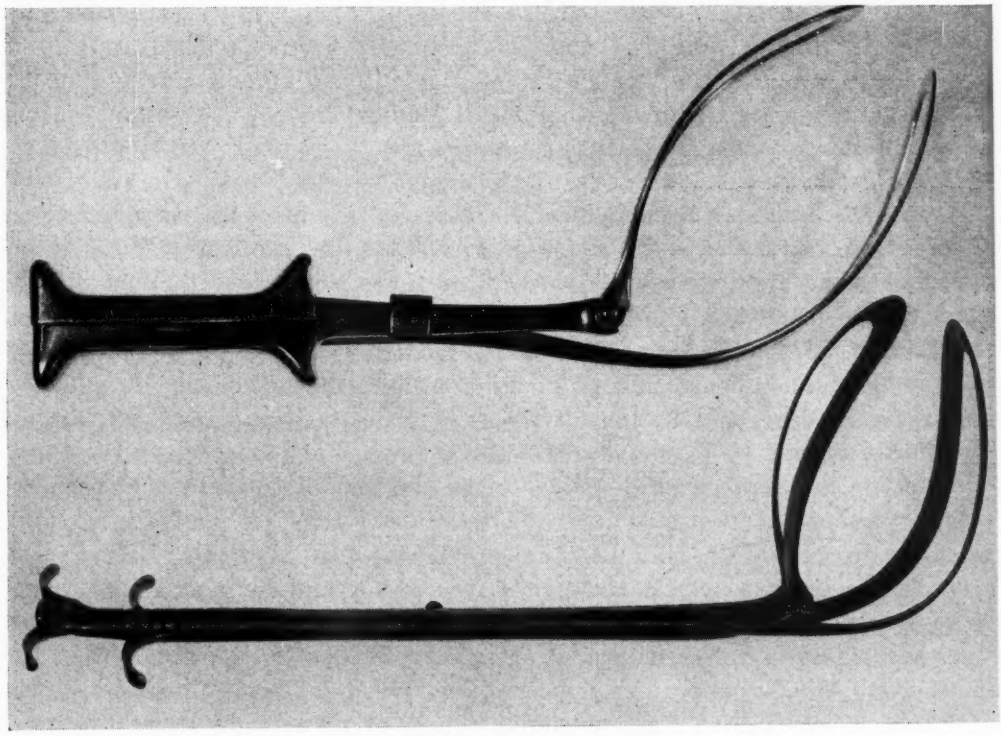


Fig. 1.—*Above,* The Barton forceps, model number 2.
Below, Farabeuf's *prehenseur-levier-mensurateur.* Note the hinged anterior blade on both instruments. (From the forceps museum of the Sloane Hospital for Women.)

This is one of the methods recommended at the present time for application of the anterior blade of the Barton forceps and is probably the first written record of this method of forceps application.

In 1893, Murdoch Cameron,[3] also of Glasgow, devised an anteroposterior forceps with axis traction. The two blades were applied to the biparietal of

the fetal head in the transverse position. Cameron said he designed the forceps particularly for markedly contracted pelvis.

Two years later, in 1895,[9] L. H. Farabeuf introduced his "cephalometer" or *prehenseur-levier-mensurateur*. This instrument most closely resembles the Barton forceps in mechanical design, since it has a hinged anterior blade and a fixed posterior blade curved to fit the sacrum. Both instruments have straight parallel shanks (Fig. 1). The chief use of the "cephalometer" was, as the name implies, for measuring the fetal head size and acting as a lever. Apparently[8] the possibility of using such an instrument as a traction forceps did not occur to Farabeuf.

No other forceps designed for anteroposterior application were described until Barton introduced his instrument in the latter part of the second decade of this century.

Lyman Guy Barton[9, 18] was born on July 1, 1866, in Willsboro, N. Y., the son of Dr. Lyman and Minerva Barton. He received his early education in the New York State public schools and graduated from Granville Military Academy in 1883. The same year he entered Cornell University on a State Scholarship and studied mechanical engineering for three years. At the end of this time, at the request of his father, Barton gave up engineering and began the study of medicine at Dartmouth Medical School, his father's Alma Mater. After leaving Dartmouth he entered Bellevue Hospital Medical College and graduated in 1891. One of his classmates was Dr. W. E. Studdiford, Sr., who was Barton's lifelong friend and in later years was instrumental in proving the usefulness of the Barton forceps. After graduation Dr. Barton returned to the Champlain Valley area of northern New York and immediately took over his father's practice. He remained in active practice in this area for the next 53 years. During his life, besides carrying the burden of a large practice, he found time to invent 14 different surgical instruments in addition to his outstanding contribution of the Barton obstetric forceps. Dr. Barton died in Plattsburg, N. Y., on Nov. 21, 1944, at the age of 78.

During the years near the turn of the century when obstetrical patients received no prenatal care and the physician was consulted only in cases of hemorrhage, eclampsia, and prolonged and difficult labor, Dr. Barton conceived the idea of a special obstetrical forceps for midpelvic and high transverse arrests. Apparently the idea for his instrument arose from "observing that dentists use a different type of extracting forceps for the molars than for the incisors."[8] He believed that deliveries were attempted in the upper pelvis with forceps which were designed for the lower pelvis and which could be used to best advantage only at this point. He also believed that there should be an entirely different mechanical principle in forceps intended for these difficult high or midpelvic applications.

With these ideas in mind Dr. Barton probably made the first drawing of his forceps around 1907. In a personal letter written in 1927 to Dr. Carl Bachman of the University of Pennsylvania in Philadelphia, Dr. Barton[10] gives a very interesting account of the development of his forceps and the dates of its first use. An extract of this letter is quoted below.

"As to the original dates, I would say that the idea of constructing a forceps with the blades at an angle to the shanks occurred to me over 20 years ago. [1907] A rather crude model was constructed and I had a conference with the late Professor Cragin of Columbia University, in regard to this modification of the forceps. His opinion was that while the idea might be correct in theory it would not work out in actual practice. Acting on his advice, I did nothing further with the forceps until 14 years ago. [1913] At that time I had drawings of the perfected instrument and these were given to Professor Studdiford for his opinion. He agreed with Professor Cragin and consequently the project was again abandoned.

"In 1924 I exhibited a drawing of the forceps to Dr. A. D. Campbell of Montreal who at once grasped the significance of the design and advised me to have the forceps made at once.

"The first pair was completed about the middle of October, 1924. Professor Studdiford had in some way heard of it and asked me to show the forceps to him as soon as completed.

"During the Clinical Congress of The American College of Surgeons held in New York City in October, 1924, I exhibited them to both Professor Studdiford and Dr. Caldwell. Both were very skeptical as to their value, but finally to settle the question they decided to see what could be accomplished with a manikin. Dr. Caldwell was the first to experiment with them and much to his surprise he found that they were easy to apply and effective in delivery.

"The first actual case in which they were used was during the first week in December, 1924. They were exhibited at the Sloane Maternity at a meeting of the American Gynecological Club in February, 1925. At that time I think they had been used in fourteen difficult cases. I have not heard from Dr. Caldwell in regard to their use at Sloane since December, 1926. At that time there had been 100 cases at that institution."

The date of the use of the forceps for the first time is not stated accurately in Dr. Barton's letter to Dr. Bachman. Recently the chart, including the labor and delivery record, of the first living patient on whom the Barton forceps was used has been located in the records of the Sloane Hospital for Women. The exact date of delivery was 7:51 A.M. on Nov. 24, 1924.

Because of the historical interest of this case it is briefly presented here.

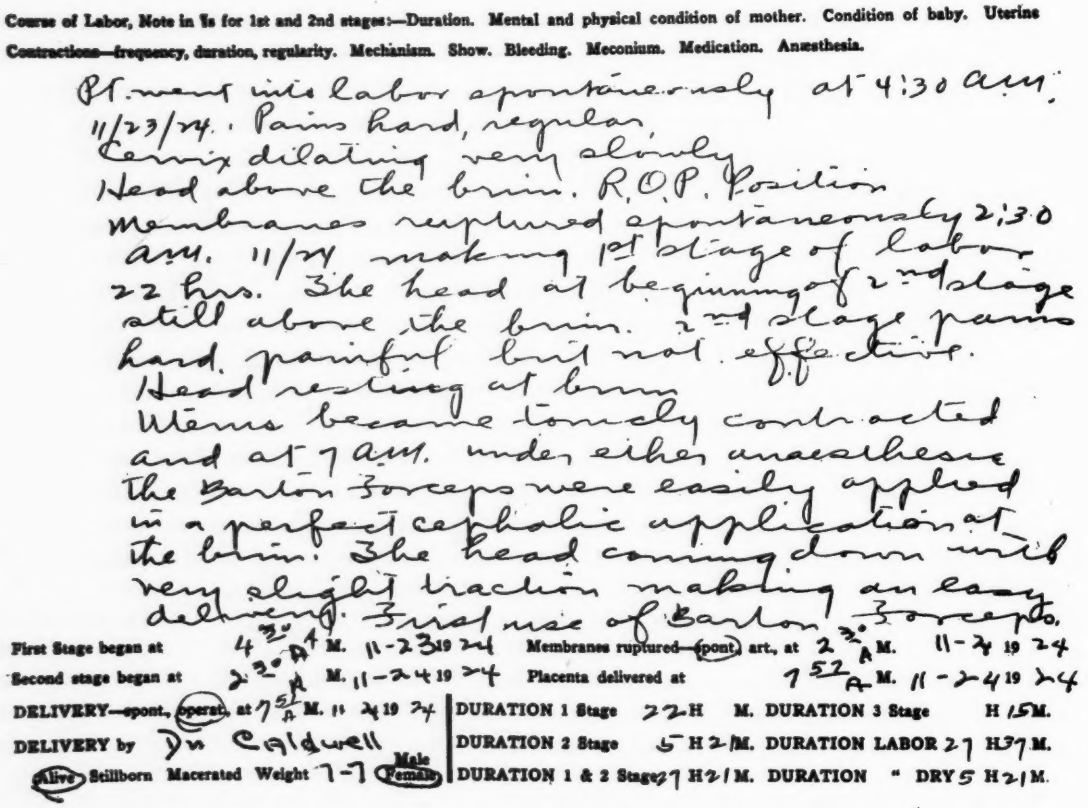
The patient, Mrs. M. G. (No. 6442)[12] was a private patient of Dr. W. E. Caldwell's. She was a 35-year-old para i, gravida ii, whose due date was about Nov. 4, 1924. One previous delivery resulted, after 48 hours of labor, in a breech delivery of a fetal monstrosity that was stillborn. The antepartum course in this pregnancy was uneventful and Dr. Caldwell typed the pelvis as "normal." On Nov. 20, 1924, the patient "felt well" and the head was "still floating." This was the last office visit the patient made before labor and the remainder of the story can best be told by reading Dr. Caldwell's delivery note (Fig. 2).

"Patient went into labor spontaneously at 4:30 A.M. 11/23/24. Pains hard, regular. Cervix dilating very slowly. Head above the brim R.O.P. position. Membranes ruptured spontaneously 2:30 A.M. 11/24 making 1st stage of labor 22 hrs. The head at beginning of 2nd stage still above the brim. 2nd stage pains hard, painful but not effective. Head resting at brim. Uterus became tonically contracted and at 7 A.M. under ether anesthesia the Barton forceps were easily applied in a perfect cephalic application at the brim. The head coming down with very slight traction making an easy delivery. First use of Barton forceps."

The infant was a 7 pound, 7 ounce normal female and both the mother and child had an uneventful course in the hospital. The patient was discharged on the fourteenth postpartum day.

On Nov. 25, 1924, the day after this high forceps delivery with the Barton forceps, Dr. Caldwell[13] wrote Dr. Barton the following:

"The forceps work! After considerable practice on the manikin we have had a case suitable for their use and found their application easy and most effective in the delivery of the child." Dr. Caldwell also added, "I congratulate you on inventing a new, and, I believe, a very serviceable forceps for use by expert hands, and we will be very glad to give you our experience with the forceps when the time comes to present the instrument to the profession."



Course of Labor, Note in ¼s for 1st and 2nd stages:—Duration. Mental and physical condition of mother. Condition of baby. Uterine Contractions—frequency, duration, regularity. Mechanism. Show. Bleeding. Meconium. Medication. Anæsthesia.

Pt. went into labor spontaneously at 4:30 A.M. 11/23/24. Pains hard, regular. Cervix dilating very slowly. Head above the brim. R.O.P. Position. Membranes ruptured spontaneously 2:30 A.M. 11/24 making 1st stage of labor 22 hrs. The head at beginning of 2nd stage still above the brim. 2nd stage pains hard, painful but not effective. Head resting at brim. Uterus became tonically contracted and at 7 A.M. under either anaesthesia the Barton forceps were easily applied in a perfect cephalic application at the brim. The head coming down with very slight traction making an easy delivery. Trial use of Barton forceps.

First Stage began at 4:30 A.M. 11-23 19 24 Membranes ruptured—spont. art., at 2:30 A.M. 11-24 19 24

Second stage began at 2:30 A.M. 11-24 19 24 Placenta delivered at 7:52 A.M. 11-24 19 24

DELIVERY—spont., operat. at 7:51 A.M. 11-24 19 24 DURATION 1 Stage 22 H M. DURATION 3 Stage H 15 M.

DELIVERY by Dr Caldwell DURATION 2 Stage 5 H 2 M. DURATION LABOR 27 H 37 M.

Alive Stillborn Macerated Weight 7-7 Male Female DURATION 1 & 2 Stage 27 H 21 M. DURATION " DRY 5 H 21 M.

Fig. 2.—Delivery note describing the first use of the Barton obstetric forceps (Sloane Hospital for Women, New York).

Considerable effort was made to collect a series of cases which could be reported before the forceps was released for general use. Ten pairs of forceps were made by George Tiemann and Company of New York and completed the last week of March, 1925.[14]

Dr. Caldwell[14] wrote Dr. Barton at this time:

"Would it be well for the present to confine the distribution of the forceps to experts such as Hirst, Polak and Chipman until we have all had an opportunity to try them out and prove their efficacy in a certain class of cases?"

The late Barton Cooke Hirst, who was Professor of Obstetrics at the University of Pennsylvania until June, 1927, had seen the forceps demonstrated in February, 1925, at the American Gynecological Club in New York and was quite enthusiastic about their possibilities. He obtained one of the ten new instruments and used it first in Philadelphia in April, 1925. Dr. Hirst's resident, Dr. Carl Bachman,[11] the present Professor of Obstetrics at the University of Pennsylvania, learned the technique of application from Dr. Hirst and saw Dr. William E. Studdiford demonstrate the forceps at a meeting of the Obstetrical Society of Philadelphia on May 7, 1925. Dr. Bachman published the first clinical report of the use of the instrument in December, 1927.[10]

The completed instrument was first officially presented at a meeting of the New York Obstetrical Society on Nov. 10, 1925.[9] However, no note was made of this event in the published transactions of the meeting.[17]

In January, 1928, the month following Bachman's publication, Barton, Caldwell, and Studdiford[8] published their clinical experience with the forceps in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

The chief defect with the early model was the tendency of the forceps to slip with strong traction. Dr. Caldwell[15] told Dr. Barton of this defect in a letter on April 30, 1925. Permission was given by Dr. Barton to lengthen the anterior blade one-half inch which obviated this difficulty.

Unfortunately[8] the original model was the one which most practictioners had in their possession and this one fact probably led to many of the failed forceps deliveries and fetal injuries which subsequently caused the forceps to be abandoned in many institutions.

The first mention of the use of an axis traction bar was made by Dr. Caldwell[16] in a letter to Dr. Barton on Dec. 7, 1926. The bar had apparently been developed by Dr. Barton some time earlier and Dr. Caldwell said of it, "we have been using the axis traction on the manikin and on several cases and everyone is very enthusiastic." The axis traction has since proved of great value in directing the traction forces accurately and is an indispensable accessory to the forceps.

Time has leavened the enthusiasm with which the Barton forceps was initially received. The high forceps has been abandoned, and rightly so. Despite the modification of the method of management of arrested transverse positions of the occiput in borderline pelves, Barton's instrument still maintains its position as a useful, specialized forceps for deep transverse arrest in patients without cephalopelvic disproportion.

References

1. Das, Kedarnath: Obstetric Forceps, Its History and Evolution, St. Louis, 1929, The C. V. Mosby Company, p. 272.
2. Das, Kedarnath: Obstetric Forceps, Its History and Evolution, St. Louis, 1929, The C. V. Mosby Company, p. 502.
3. Das, Kedarnath: Obstetric Forceps, Its History and Evolution, St. Louis, 1929, The C. V. Mosby Company, p. 627.
4. Baumers, R.: Bull. Soc. de méd. de Gand, 16: 236, 1849.
5. Sloan, S.: Brit. M. J. Lond. 1: 229, 1889.

6. Fry, H. D.: Am. J. Obst. **22**: 1165, 1889.
7. Cacciarelli, R. A.: Forceps in Obstetrics, privately printed, 1949.
8. Barton, L. G., Caldwell, W. E., and Studdiford, W. E.: AM. J. OBST. & GYNEC. **15**: 16, 1928.
9. Dossert, F. C., editor: The Barton Forceps, privately printed, 1949.
10. Bachman, Carl: Surg., Gynec. & Obst. **45**: 805, 1927.
11. Bachman, Carl: Personal communication.
12. Sloane Maternity Hospital, Chart No. 6442.
13. Barton-Caldwell Correspondence, Nov. 25, 1924.
14. Barton-Caldwell Correspondence, March 21, 1925.
15. Barton-Caldwell Correspondence, April 30, 1925.
16. Barton-Caldwell Correspondence, Dec. 7, 1926.
17. Transactions, New York Obstetrical Society: AM. J. OBST. & GYNEC. **11**: 688, 1926.
18. Porter, Mrs. M. L.: New York State J. Med. **45**: 1094, 1945.
19. Decker, W., and Heaton, C.: AM. J. OBST. & GYNEC. **61**: 635, 1951.

ENDOCRINE ALLERGY AND THE THERAPEUTIC USE OF PREGNANDIOL

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IT HAS been postulated that many of the disorders related to ovarian function are associated with an endogenous allergy to steroid hormones and related substances.[1] These disorders include the ovarian pain syndrome[2] (congestion-fibrosis syndrome,[3] pelvic sympathetic syndrome[4]), painful breasts and chronic cystic mastitis, menopausal symptoms, premenstrual distress (tension), and other phenomena associated with the menstrual cycle. To test this hypothesis pregnandiol has been used as a hyposensitizing agent in the treatment of these conditions.[5] This substance, a metabolic product of progesterone, was chosen because in an earlier study[1] skin testing with various steroids of patients having these disorders showed that most of them were sensitive to it. There were positive reactions to pregnandiol in 74 per cent of women with premenstrual distress, in 60 per cent of those with painful breasts, in 56 per cent of patients with menopausal symptoms, and in 56 per cent of patients with the ovarian pain syndrome. More recent experience with skin tests, using microcrystalline suspensions in an aqueous medium of cortisone, estradiol, estrone, pregnenolone, progesterone, and testosterone in addition to pregnandiol, indicates that an even greater proportion of patients with these conditions are sensitive to this steroid. Pregnandiol has no known biological activity in man.

A therapeutic technique comparable to treatment of endocrine allergy with pregnandiol would be the treatment of all patients with early summer hay fever (grass pollinosis), in the northeastern United States with timothy pollen. Most sufferers from grass pollinosis would be sensitive to timothy and because of the antigenic similarity of the pollens, extract of timothy pollen would hyposensitize many of the patients sensitive to other grasses.

Endocrine allergy is a new concept. Zondek and Bromberg[6] in 1947 demonstrated it in certain pathological conditions related to menstruation and the menopause. Because of the difficulties in showing sensitivity to steroids by skin test, they concluded that endocrine allergic conditions are not frequent. On the theory that if endogenous allergy exists it should not be unusual since the conditions with which it was shown to be associated are common, skin testing was done using other vehicles than the olive oil used by Zondek and Bromberg for solution or suspension of the steroids.[1] This study showed that the majority of women with frequently occurring disorders associated with the menstrual cycle and the climacteric gave evidence of sensitivity to steroid hor-

mones and related compounds both by skin reactions and by the production or aggravation of their symptoms by steroids which produced positive skin tests.

Systemic Reactions

Evaluation of treatment is always difficult when the desired result is the relief of subjective symptoms. Thus, evaluation of the treatment of menopausal symptoms with estrogens, for example, is always vulnerable to the skepticism of those who would attribute the beneficial results largely to suggestion. No thoughtful clinician would deny the importance of suggestion in any treatment, and controlled studies indicate that 20 to 25 per cent of patients with menopausal symptoms may be relieved by placebos.[7]

TABLE I. ANALYSIS OF DAILY ORAL DOSAGE OF PREGNANDIOL (108 CASES TREATED WITH TABLETS ALONE)

	IN CASES IMPROVED ON A CONSTANT DOSE			IN CASES IMPROVED IN WHICH THE DOSE WAS CHANGED			IN CASES WHERE TREATMENT FAILED ON A CONSTANT DOSE			IN CASES WHERE TREATMENT FAILED ALTHOUGH THE DOSE WAS CHANGED		
	1.0 MG.	0.5 MG.	0.1 MG.	1.0 MG.	0.5 MG.	0.1 MG.	1.0 MG.	0.5 MG.	0.1 MG.	1.0 MG.	0.5 MG.	0.1 MG.
Number of times dose was used	19	8	9	17	14	13	11	5	1	10	4	11
Number of times dose caused a systemic reaction	3	0	0	5	3	3	6	2	1	10	1	4

The figures show that systemic reactions (aggravation of symptoms or production of new symptoms) were proportional to the dose.

Tablets were prescribed for at least a month. In some cases the dose was increased if there was no effect or decreased if a systemic reaction occurred.

If a systemic reaction was transient the same dose might be continued.

TABLE II. SUMMARY OF ORAL DOSAGE IN CASES IN WHICH IT WAS BENEFICIAL AND IN WHICH SUBCUTANEOUS TREATMENT WAS ALSO TRIED (47 CASES)

	1.0 MG.	0.5 MG.	0.1 MG.
Number of times dose was used	24	16	28
Number of times dose caused a systemic reaction	5	0	1

In these cases it was possible to evaluate oral treatment although subcutaneous injections were also given, usually initially as a test dose. All patients were relieved. Systemic reactions were proportional to the dose.

An important phenomenon in the present study, and one which lends great support to the allergy hypothesis, is the occurrence of systemic or constitutional reactions. The term *systemic reaction* is used to indicate the production or aggravation of symptoms which the patient has been experiencing or the production of symptoms not previously noted. Analysis of the results of both oral and subcutaneous treatment reveals that systemic reactions occurred in all of the clinical categories, premenstrual distress, climacteric, etc., and that they were proportional to the dose; the larger the dose the more frequent and severe were these reactions (Tables I, II, III, V). Typical manifestations were as follows: The patient might feel worse about three hours after an injection. One or several symptoms such as pelvic pain, fatigue,

dizziness, and nausea would be increased. Within 24 hours a local reaction might be apparent (see Case 3 and Fig. 1). Within 24 or 48 hours the patient might feel better than she had when the injection was given. Another reaction might be that symptoms which the patient was not experiencing at the time would be produced in a few hours and a new symptom might appear. Tension and nervousness might predominate, with irritability and insomnia. This was most striking in cases of premenstrual distress treated early in the cycle. Similar reactions were obtained with oral treatment although their appearance was less sudden and dramatic. New symptoms, those not previously noted by the patient, were usually those which are common in the

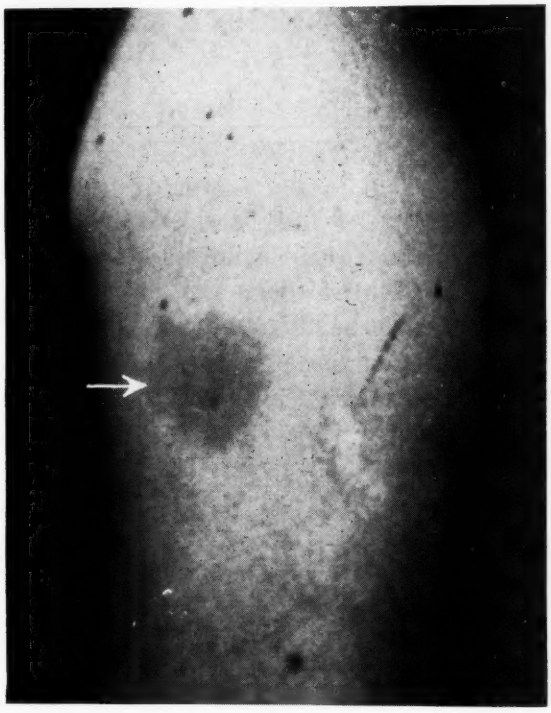


Fig. 1 (Case 3).—Local reaction of the skin of the arm 24 hours after subcutaneous injection of 0.1 mg. of pregnandiol in aqueous suspension, 0.1 c.c. Reactions of this magnitude are unusual. Slight induration and tenderness noted by palpation of the area in 24 or 48 hours are common.

various syndromes. The more common in order of frequency were nausea, dizziness, headache, pelvic pain, pain in the breasts, hot flashes, and nervousness. Occasionally a feeling of malaise was described.

Administration and Dosage

It was clear from the earlier study that hyposensitization by subcutaneous injections was a useful procedure. Its success supported the allergy hypothesis. The initial subcutaneous dose of pregnandiol* was usually 0.1 mg. in 0.1

*Paper chromatographic assay by Dr. Leonard Axelrod of the pregnandiol used in this study shows approximately twice as much pregnandiol 3-alpha 20-alpha as allopregnandiol 3-alpha 20-alpha and a small amount, 3 to 5 per cent by weight, of allopregnandiol 3-beta 20-alpha. Any other isomeric forms, if present, are in amounts less than 1 per cent by weight of the samples analyzed. Several sensitive patients have been skin tested simultaneously with this preparation and with pure pregnandiol 3-alpha 20-alpha. Reactions were the same.

c.c. Microcrystalline aqueous suspensions were used. As in skin testing with steroid substances, injection was made just under the dense portion of the skin, not intracutaneously.[6, 1] Because of the relative inconvenience of subcutaneous treatment, particularly in mild cases, oral treatment was also tried. Doses of 0.1, 0.5, and 1.0 mg. were arbitrarily chosen.

TABLE III. SUBCUTANEOUS DOSES USED IN HYPOSENSITIZATION AND FREQUENCY OF SYSTEMIC REACTIONS (64 CASES TREATED SUCCESSFULLY)

	0.1 MG.	0.01 MG.	0.005 MG.	0.001 MG.	0.0005 MG.	0.0001 MG.	0.00005 MG.	0.00001 MG.	0.000005 MG.
Number of cases in which dose was used successfully	6	28	5	13	3	5	1	2	1
Number of times dose produced a systemic reaction	19	8	1	4	0	0	0	0	0

The doses were administered in microcrystalline aqueous suspension, 0.1 c.c.

Analysis of results in Tables I, II, and III reveals that doses were too large. Overdosage caused some of the failures. Smaller amounts of pregnandiol are presently being used. Oral doses are now 0.01, 0.05 or 0.1 mg. daily and subcutaneous treatment is begun with higher dilutions. Local and systemic reactions to smaller subcutaneous doses than indicated in Table III have now been observed. Less than about 5 micrograms of pregnandiol, 0.005 mg., cannot be detected chemically, yet calculation disclosed that 0.0000001 mg., 10^{-7} mg., of pregnandiol contains nearly 200 billion molecules (1.882×10^{11}).

CASE 1 (No. 1943).—This patient experienced dramatic improvement with 10^{-7} mg. after experiencing a systemic reaction with 10^{-5} mg. This case of premenstrual distress, including tension, irritability, depression, fatigue, and painful breasts was relieved by oral pregnandiol for eight months after which symptoms began to increase. The initial dose had been 1.0 mg. and it had been increased to 2.0 mg. daily. Decreasing the oral dose to 0.1 mg. was unsuccessful. Malaise, nausea, occipital headache, and chest pain were produced by a test dose of 0.01 mg. subcutaneously. The dose of 10^{-7} mg. was then arrived at and has been remarkably successful.

This is an example of decreasing tolerance. A similar phenomenon is observed in the treatment of pollinosis during the season when pollen is in the air.[8]

Detailed analysis of dosage in the various categories was made not only to determine the optimum dose, but to see if there was any major difference in the response to treatment among the categories. According to the hypothesis, all of them, ovarian pain, premenstrual distress, menopausal symptoms, etc., may result from endocrine allergy. There was little difference in response in the various categories. The smaller doses by either route are beneficial without as much risk of systemic reactions.

Hyposensitization.—A dose was chosen smaller than that which produced any reaction. If 0.1 mg. by mouth produced symptoms, the subcutaneous

route was resorted to. Patients who seemed to be unusually sensitive (see Case 4) were given subcutaneous treatment immediately because it is more easily evaluated and controlled.

Frequently an initial subcutaneous dose of 0.1 mg. in 0.1 c.c. caused a local and/or a systemic reaction. Local reactions, apparent in 24 hours, ranged from slight induration and tenderness to an inflamed wheal like that shown in Fig. 1. Higher dilutions, 0.01 mg. or some fraction thereof in 0.1 c.c., were then tried. When the most concentrated solution which produced no reaction was found, patients were given directions for self-treatment daily or every other day. If local or systemic reactions were experienced during treatment the concentration was further decreased.* Serious reactions have not been observed. The volume of the injection, 0.1 c.c., was always the same. Table III shows dilutions used as well as the frequency of systemic reactions.

Results of Treatment

Over-all results of treatment without regard to route of administration are shown in Table IV. There are 254 cases, 52 of which were included in the first study.[1] *Improved* means that there was relief of symptoms attributable to the treatment. Successful oral treatment was continued from one to several months. Subcutaneous hyposensitization was usually continued for a number of months. L. S., Case 3 in the earlier study,[1] continues to take subcutaneous injections of 0.0005 mg. of pregnandiol in aqueous suspension regularly three years after beginning treatment. Some patients take pregnandiol only occasionally for relief of symptoms (Case 3).

TABLE IV. OVER-ALL RESULTS OF TREATMENT WITH PREGNANDIOL

	TOTAL NUMBER OF CASES	IMPROVED	
		TOTAL	%
Premenstrual distress	67	54	81
Climacteric	66	51	79
Ovarian pain syndrome	60	44	73
Painful breasts and chronic cystic mastitis	24	16	67
Endometriosis	6	5*	83
Headache related to menstrual cycle	9	6	66
Hypogonadism	11	9*	82
Acne	5	5	100
Other dermatoses	6	2	33
Total	254	192	76

*Relief of symptoms.

Oral treatment alone was 71 per cent effective (Table V). Eighty-two per cent of 33 patients classed as menopausal (climacteric) were relieved. This compares favorably with reported results of treatment with oral estrogens,[9] and side effects, such as endometrial growth and subsequent bleeding, need not be feared.

CASE 2 (No. 2282).—This is a 54-year-old woman who after three months' amenorrhea began to have slight vaginal bleeding. When, nearly three months later, the bleeding became

*The skin is a variable indicator of sensitivity to steroids.[1] Systemic reactions are more reliable criteria of overdosage.

heavy a curettage was done. An atypical hyperplasia with the appearance of possible early carcinoma was found and a hysterectomy was planned. It was then discovered that the patient had been taking 0.05 mg. of ethinyl estradiol daily for seven or eight months because of menopausal symptoms consisting principally of cardiac palpitations and anxiety. In spite of the treatment, palpitations had continued and she was nervous and anxious. The hysterectomy was cancelled and she was given pregnandiol, 0.1 mg. daily, in place of the estrogen. A month later she reported a "great change." She was no longer so nervous (her husband had remarked about this) and her anxiety had disappeared.

Three months later she had had no bleeding and reported only occasional hot flashes and palpitations. She noted that when she had hot flashes there were no palpitations and vice versa. They never occurred together.

This behavior of symptoms suggests *alternation of shock organs,* an allergic phenomenon. It was noted in all the categories, notably the ovarian pain syndrome. One symptom or group of symptoms might be replaced by another symptom or symptom complex and then appear again when the second had disappeared.

TABLE V. ORAL TREATMENT ALONE

	NUMBER OF CASES	CASES RELIEVED			FAILURES	
		NO.	%	PER CENT SHOWING SYSTEMIC REACTIONS	NO.	PER CENT SHOWING SYSTEMIC REACTIONS
Premenstrual distress	26	15	58	8	11	55
Climacteric	33	27	82	9	6	50
Ovarian pain syndrome	28	21	75	11	7	86
Painful breasts and chronic cystic mastitis	11	6	55	18	5	40
Endometriosis	4	3*	75	0	1	100
Headache	3	3	100	0	0	
Hypogonadism	3	2*	67	67	1	100
Total	108	77	71	16	31	61

*Relief of symptoms.

Many patients treated orally were initially given 0.1 or 0.01 mg. in 0.1 c.c. subcutaneously as a test dose. One injection frequently resulted in relief of symptoms. It was possible, however, to evaluate subsequent oral treatment in 47 of these patients, and they were analyzed separately from those who received only oral treatment (Table II). In 39 cases it was possible to evaluate the isolated doses of 0.1 or 0.01 mg. Improvement was attributable to the single injection in 61 per cent. Twenty-three per cent experienced systemic reactions. This remarkable improvement following a single dose of a substance to which the patient is allergic and to which she is reacting has been observed in the treatment of allergy to pollens. Rackemann[8] states, "In 1928 Vaughan advised the continuation of treatment into the pollen season, and now we recognize not only that this continuation of the pre-seasonal treatment is helpful, but also that treatment started in the season itself, after symptoms have begun, often gives very gratifying results. We learn that each dose may have a striking effect. I have seen an injection of pollen extract clear the symptoms almost as well and as promptly as a 'shot' of epinephrine."

Of cases in which both oral and subcutaneous treatment were used and in which the former had failed, 67 per cent were relieved by hyposensitization

with the use of small subcutaneous doses (Table VI). The over-all benefit from subcutaneous hyposensitization was 84 per cent (Table VII).

TABLE VI. CASES GIVEN REPEATED SMALL SUBCUTANEOUS INJECTIONS IN WHICH ORAL TREATMENT HAD FAILED

		CASES RELIEVED	
	NO.	NO.	%
Premenstrual distress	16	14	88
Climacteric	19	11	58
Ovarian pain syndrome	17	11	65
Painful breasts and chronic cystic mastitis	10	6	60
Endometriosis	0		
Headache related to the menstrual cycle	2	0	0
Hypogonadism	5	3*	60
Total	69	45	67

*Relief of symptoms.

TABLE VII. TOTAL CASES HYPOSENSITIZED BY REPEATED SMALL SUBCUTANEOUS INJECTIONS

		CASES RELIEVED	
	NO.	NO.	%
Premenstrual distress	30	27	90
Climacteric	10	8	80
Ovarian pain syndrome	18	16	89
Painful breasts and chronic cystic mastitis	10	7	70
Endometriosis	1	1*	100
Headache related to the menstrual cycle	4	2	50
Hypogonadism	3	3*	100
Total	76	64	84

*Relief of symptoms.

CASE 3 (No. 2241).—A 23-year-old woman began to have right lower quadrant pain eight months after the normal termination of her first pregnancy. The pain began about two weeks before menstruation and continued until the onset of flow. It was accompanied by pain in the bladder which preceded the urge to urinate, intestinal cramps preceding bowel movements, bloating, irritability, insomnia, low backache, a sensation of cold, and marked fatigue. There was constipation also for two weeks before menstruation, but three days before the onset of the flow diarrhea occurred. Menstruation had been preceded by about four days of spotting since symptoms began. She was seen on the tenth day of the fifth menstrual cycle following the onset of these symptoms. During the previous menstrual cycle dizziness had been experienced in addition to her other complaints.

General physical findings were negative; blood pressure was 110/70, hemoglobin 14 Gm., blood cholesterol concentration 275 mg. per cent. Pelvic examination revealed normal findings except for unusual tenderness of the right ovary, which was estimated at 3 to 4 by 2 by 2 cm. The patient was feeling very well as usual in the early part of the cycle. Since recent cycles had been thirty-one or thirty-two days in length, she expected to continue to feel well for another six or eight days.

The patient was given 0.1 mg. of crystalline pregnandiol in 0.1 c.c. of an aqueous suspension subcutaneously at about 3 o'clock in the afternoon. In the evening around 9 o'clock the patient began to have right lower quadrant pain. This was followed by the pain in the bladder and flushing of the head and neck. She became dizzy. Hot flashes continued through the night and she was restless. In the morning intestinal cramps preceded her bowel movement. When she was seen 24 hours after the injection she complained only of fatigue. At the site of the subcutaneous injection of pregnandiol there was a red wheal 3 cm. in diameter (Fig. 1). She then took 0.5 mg. of pregnandiol by mouth daily for four days. She took the tablets in the morning. Each afternoon at about 5 o'clock the skin test itched and became red. This ceased when she stopped the tablets. A fraction of a tablet, about 0.025 mg.,

was now tried. This resulted in only slight itching at the site of the injection, where a hard lump 1 to 2 cm. in diameter remained for a month or more. On the twenty-second day of the cycle her symptoms suddenly recurred. They cleared within 12 hours after 2.0 mg. of estradiol dipropionate was given intramuscularly. The attack lasted about 36 hours in all. (Large doses of steroids, particularly estrogen, to which the patient is not sensitive may be beneficial.[1]) Pregnandiol in aqueous suspension 0.0001 mg. was given on the twenty-sixth day of the cycle. Normal menstruation, without prodromal symptoms or spotting, began on the thirtieth day.

During the subsequent five months the patient had two rather mild recurrences of symptoms. One occurred on the seventeenth day of the cycle, the other on the nineteenth. Each time symptoms were alleviated by subcutaneous injections of 0.001 or 0.0001 mg. of crystalline pregnandiol. On at least two occasions there was mild right lower quadrant pain for two days before menstruation.

Flare-up of previous skin tests is noted from time to time after administration of pregnandiol. It is one manifestation of sensitivity. These recurrent reactions may occur spontaneously in midcycle or premenstrually. They were more frequent and they occurred for a much longer time after the original injection when the steroids were administered in oil.[1] They have been observed as long as three years after the original tests.

Cases 3, 5, and 6 are examples of the ovarian pain syndrome. This frequently seen symptom complex has received in recent years some of the attention it deserves.[2, 3, 4] The term ovarian pain syndrome[2] is used because it is descriptive rather than implying etiology, and because it calls attention to the importance of the ovaries, one of which is usually the focus of pelvic pain. Removal of the painful ovary, a procedure all too often carried out, results not in any lasting amelioration but in ultimate aggravation of the condition. The term *congestion-fibrosis syndrome*[3] is perhaps the most familiar among American gynecologists. Other recent names are *pelvic sympathetic syndrome*[4] and *pelvic hyperemic syndrome.*[10] In the following case symptoms were not typical for any one of the categories, and no association with the menstrual cycle was noted by the patient.

CASE 4 (No. 1931).—A 21-year-old woman, para ii, began to have nausea, dizziness, and constipation, alternating with diarrhea, after the birth of her first baby twenty-seven months before. No improvement occurred during or after her second pregnancy, which resulted in delivery of a normal child at nine months. She had nausea most of the time. The pelvic outlet was tender to such a degree that coitus was practically impossible. She had puffiness of the hands, particularly in the morning, pain in both lower quadrants, greater on the left. She had noticed no relationship of these symptoms to her menstrual cycle. Just before her marriage three years before she suddenly developed pain and swelling in the left side of the chest. It was apparently in the region of the clavicle and along the left edge of the sternum.

On examination the pelvic outlet appeared relaxed and the vaginal mucous membrane was more red than normal. Vaginal smear showed cornified epithelial cells and white blood cells. The uterus was normal in size. There was tenderness on the left.

The history suggested endocrine allergy, but since the appearance of the genitals suggested hypoestrinism, ethinyl estradiol, 0.05 mg. daily, was prescribed. She took only two of these tablets because they increased the nausea.

Four months later she was seen again. There had been no improvement. Pain was now greater on the right side and she complained of abdominal bloating. She had vomited two or three times in the past three weeks and nausea was constant. The left breast was tender but not painful. She felt dizzy when she moved. Coitus was still impossible because

of tenderness. An injection of pregnandiol, 0.01 mg. was given subcutaneously. Within three hours severe nausea and frontal headache began. Headache lasted about six hours; nausea persisted longer. A dose of 0.0001 mg. of pregnandiol produced no reaction. For a month the patient injected under the skin 0.0001 mg. in 0.1 c.c. of an aqueous suspension every other day. Nausea cleared completely and other symptoms decreased, including the vulval soreness (uterine and adnexal tenderness are common, vulval and vaginal involvement less so).

Following a menstrual period six weeks later, which was heavier and shorter than usual, nausea began again. Two weeks after this, pelvic findings were normal except for uterine tenderness which was less than before treatment. There was again prompt improvement when injections of pregnandiol, 0.0001 mg., were resumed.

CASE 5 (No. 2265).—A 34-year-old woman complained of pelvic and abdominal pain extending from the right lower quadrant up under the costal margin and into the right flank. The present attack of pain began fifteen days before, six days before menstruation, which for several months had consisted only of spotting of three days' duration. She had experienced right lower quadrant pain off and on for the past three years. During the present attack pain extended up under the costal margin, into the flank, and down the thigh to the knee and upper leg. She complained of increasing fatigue; she felt exhausted. For the past two months there had been soreness of the left breast and a reeling sensation for a week before menstruation. Ten years ago an attack of pain in the right side resulted in an exploratory operation and appendectomy. Three years ago she was hospitalized for several days because of similar pain. Married fifteen years, she had had no pregnancies. Coitus had been painful recently because of vaginal and pelvic tenderness. Urological examination had revealed nothing abnormal. Pelvic diathermy had aggravated the pain. Examination revealed tenderness in the right upper quadrant and under the costal margin. The uterus was tender on pelvic examination and there was tenderness in the region of the right ovary. Neither ovary was outlined and there were no masses. Because of the unusual right upper quadrant pain a cholecystogram was obtained. This proved to be normal. Blood cholesterol concentration was 223 mg. per cent.

One-tenth mg. of an aqueous suspension of pregnandiol, 0.1 c.c., was given subcutaneously. She was seen again four days later, when she reported that she began to feel better several hours after the injection. "I can never tell you the relief I have had from the pain," was her comment. Pain, including that in the region of the gall bladder, had vanished. She had only a little bloating which she had experienced before. Local redness, induration, and tenderness of the skin had occurred within 24 hours and still covered a 2 cm. area at the site of the injection. She was given a vial of an aqueous suspension of pregnandiol, 0.01 mg. per c.c., for injection of 0.1 c.c., 0.001 mg., three times weekly. When menstruation occurred at the normal time, after five of these injections had been taken, it was of normal amount and duration, five days, for the first time in seven months. Fatigue disappeared. She felt "like a new woman," had no pain whatever, and slept better. There remained only slight premenstrual bloating of the abdomen. Three months after beginning treatment she stopped injections for a week incident to a vacation. Slight pain began in the right flank, but cleared promptly on resumption of injections. At this time, three and one-half months after treatment was begun, she stated that she believed she felt better than ever before.

CASE 6 (No. 2249).—A farmer's wife, aged 35 years, para v, the youngest child 4 years old, had long had right lower quadrant pain, worse about two days before menstruation. She also experienced marked fatigue and bloating. Six or seven years before, a curettage had been done because of similar trouble. She felt better after this for two or three months but symptoms recurred. Menstruation had become heavier with clots. During the week before her last menstrual period she had a "nervous breakdown." She was completely incapacitated with dizziness, extreme nervousness, chills, and exhaustion. She thought she was going to die. The patient was a large and well-developed woman. She appeared worried, suspicious, and hostile. General physical findings were negative. Pelvic examination revealed great tenderness of the uterus, which was normal in size. Blood cholesterol was 250 mg. per

cent. Pregnandiol, 0.01 mg. (0.1 c.c. of a suspension of 0.1 mg. per cubic centimeter) was given subcutaneously. She was supplied with material for injection of the same amount every day. Two months later she stated that she felt much better. Menstruation had been more normal. She no longer looked tense and harassed. "Pains don't bother me as long as I take those shots, but if I miss a shot I have the pains." Fatigue was less, but there was considerable bloating. Treatment was continued. Fifteen weeks after beginning injections she again said that she felt well as long as she took the "shots." There was no pain at all if she took them regularly. If the interval was longer than 48 hours she had "terrible pains" in the morning (she took the injections at night). In this event she would take an injection, usually at 6:30 A.M., and experience relief by noon. She was enthusiastic, stating that there had been nothing but improvement in the nearly four months of treatment, but she was experiencing local reactions in 24 hours and had some nervousness, restlessness at night, and generalized itching. It was suggested that the dose be decreased to 0.001 mg. A suspension of the original concentration, 0.1 mg. per cubic centimeter, was also given. Two months later she reported that the more dilute preparation was not effective. The original suspension continued to be as beneficial as before and there was no longer any local reaction.

CASE 7 (No. 2268).—The patient, aged 40 years, para ii, complained of nervousness, occasional numbness of the fingers and difficult breathing, a feeling of not being able to catch her breath. These symptoms were not related to the menstrual cycle, but she had occasional dizzy spells before menstruation. She had been depressed and tense, notably premenstrually. Breasts were usually sore for a week or so before menstruation. A basal metabolism test done a year or two before had been normal. General and pelvic examinations revealed normal findings. Blood cholesterol concentration was 315 mg. per cent. Pregnandiol, 1.0 mg. daily by mouth, was given. Four weeks later she reported that numbness and dyspnea had cleared and that she felt generally better. Ten weeks after beginning treatment she stated that she felt "100 per cent better." She had stopped taking the tablets for a week but symptoms recurred. Resuming them, she had again improved.

CASE 8 (No. 2169).—This patient, aged 34 years, complained of recurrent soreness and heaviness of the breasts for the past ten years, since shortly after marriage. Symptoms had become more troublesome and lumps had formed in the breasts, beginning two weeks before menstruation and lasting through it. In recent months occipital and frontal headaches had been occurring with menstruation and lasting for six days. Facial acne occurred before menstruation.

Examination revealed prominent, diffusely nodular glandular tissue in both breasts. The right breast was larger and more painful. Pelvic examination revealed the uterus to be retroverted, normal in size, and tender. There was definite tenderness in the region of the right ovary and some on the left.

Skin tests were done in this case. Cortisone, estradiol, estrone, pregnandiol, pregnenolone, progesterone, and testosterone, 0.1 mg. in aqueous suspensions, were given just under the dense portion of the skin. In 24 hours there were reactions to pregnandiol and progesterone, 2 plus and 1 plus, respectively. Pregnandiol, 0.5 mg. by mouth, was prescribed. Two weeks later she reported that after a few days in the latter half of the cycle she began to experience nausea after taking the tablet. Pain and tenderness of the breasts were about the same, but there was a little less heaviness on the right. Menstruation was shorter and headache lasted only three days. Facial acne was worse. The dose of oral pregnandiol was decreased to 0.1 mg. daily. A month later she reported only mild soreness of the breasts premenstrually and a headache lasting only one day. Breasts were soft and normal to palpation, with only a little tenderness. These findings were in marked contrast to those of the original examination which was also made early in the cycle. When treatment was stopped for a month she reported increased soreness of the breasts and more severe headache. Treatment, 0.1 mg. daily by mouth, was resumed for sixty days. While she was taking 0.1 mg. daily only "normal" soreness of the breasts occurred for four days before menstruation and headache occurred for only one day. When treatment was again stopped for a month, two weeks of swelling and pain in the breasts recurred and headache lasted throughout menstruation.

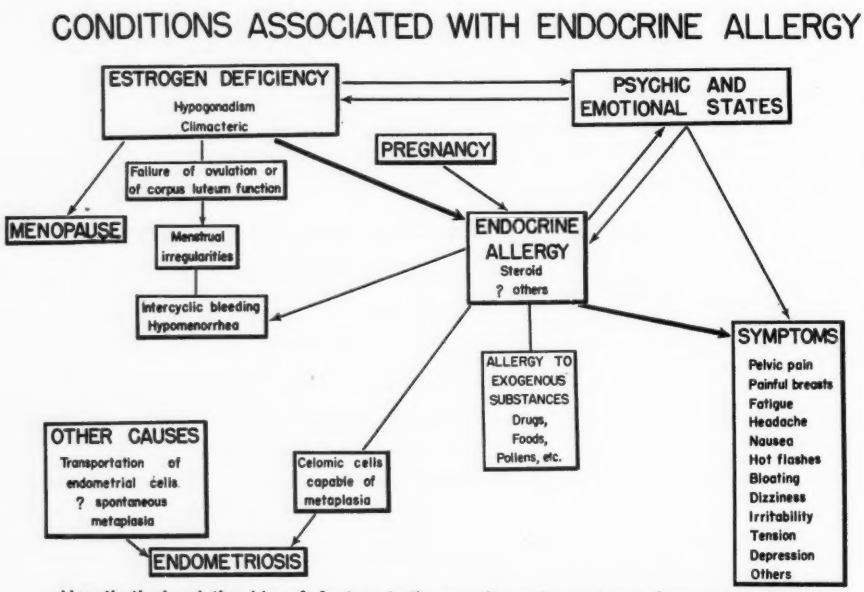
CASE 9 (No. 1722).—This patient, aged 38 years, para ii, had always had migraine occurring before or after menstruation. The pain, usually behind the right eye, occurred gradually and lasted for 24 hours, often accompanied by nausea. She had premenstrual hot flashes, and was nervous and irritable. Breasts were occasionally sore and there had been some pain in the left lower quadrant of the abdomen. Bloody spotting had occurred for ten days before her last menstruation, which was more profuse than usual. General and pelvic examinations revealed normal findings. Blood cholesterol concentration was 125 mg. per cent. Tablets of pregnandiol, 1.0 mg., one daily, were prescribed. Two weeks later she reported that a normal menstruation had occurred without her usual headache; she had had a slight one the week before. A month after this she remarked that she was much less nervous. "I don't know when I've felt so well." She had had no headache nor hot flashes. Breasts were not sore. She continued to take pregnandiol daily. Eleven months after treatment was begun she stated that her menstrual periods were "unbelievably better." She had occasional mild headaches but they did not "materialize." Cycles were regular every 28 days. She continued to feel better generally. Her husband remarked that she was a better person to live with. Breasts had been a little sore premenstrually. Three months later because of almost constant discomfort in the left breast and premenstrual soreness of both, as during pregnancy, the daily dose of pregnandiol was decreased to 0.5 mg. Five weeks later she reported that breasts were no longer sore. Now after taking 0.5 mg. for ten months, and more than two years after beginning treatment, she is without complaints and is menstruating normally.

Conditions Associated With Endocrine Allergy (Fig. 2)

As in the earlier study[1] the symptoms in the clinical categories were analyzed (Table VIII). It was again apparent that many symptoms are common in all and that the diagnosis is likely to be based on chief complaints, and in the case of the climacteric on age. Endocrine allergy appears to underlie all of them. Fig. 2 shows the hypothetical relationship of various associated conditions. A degree of ovarian failure is usually present. Sensitivity has been shown to be greater in women when estrogen is at a low level.[11, 12] The beneficial effect of estrogen in the climacteric, as generally supposed, is the result of relief of a deficiency, but it operates by making the woman less sensitive. This hypothesis is consistent with the work of Reynolds and Kaminester,[13] who produced hot flashes in menopausal women by injection of estrogen and showed that they were associated with an altered reaction, an accelerated increase in finger volume compared with that of normal women and men. In the treatment of menopausal symptoms with parenteral estrogen it is frequently noted that a patient who has been benefited may quite unexpectedly have her symptoms, hot flashes, etc., aggravated rather than relieved by the same dose of estrogenic substance which had been giving relief. Very often a woman who received benefit from parenteral estrogen will report that there is a lag of 24 or 48 hours after an injection before she has relief of symptoms or that she feels worse for a time before relief. Such patients have become unusually sensitive to estrogen so that the bad effects balance or outweigh the good. Some other steroid, progesterone, pregnenolone, or testosterone, may be beneficial. The validity of this observation is evidenced by the now widespread use of other steroids in the treatment of the climacteric.

An important observation in this series of patients, as well as in that previously reported, is that among the most troublesome cases are those of patients who have had ovarian tissue removed. These women frequently have severe symptoms which are difficult to control. Often one ovary was removed

because of the pain. As previously shown,[2] the pain may have been associated with estrogen deficiency and removal of part of the already inadequate ovarian tissue aggravated the condition. The pelvic viscera are the shock organs of steroid allergy in these cases. Aggravation of the estrogen deficiency results in increase of the allergy and increased pain. These women may continue to have pelvic pain even after total hysterectomy and bilateral salpingo-oophorectomy. The genital organs, usually one ovary, are the principal focus of the allergic reaction, but adjacent tissues may also be involved. At times bladder and ureters seem to be important foci (Case 3). Intestinal cramps may be a symptom, and, as in Case 5, pain may suggest biliary colic.



Hypothetical relationship of factors in the ovarian pain syndrome (congestion fibrosis syndrome, pelvic hyperemic syndrome), menopausal syndrome, premenstrual distress (tension) and other disorders related to the menstrual cycle.

Fig. 2.

Many women as they approach the menopause begin to have premenstrual complaints which in a younger woman would lead to a diagnosis of premenstrual distress or tension. Often a history of premenstrual distress earlier in life can be obtained. Donovan,[14] who discussed the problem of the climacteric from the psychiatric point of view, found that careful histories of these patients revealed that the symptoms were not new, but dated back many years in some cases. Premenstrual distress and menopausal symptoms are both manifestations of endocrine allergy. Estrogen deficiency at the climacteric aggravates the condition.

The importance of emotional and psychic states in allergy to steroids was pointed out in the first study.[1] That psychic and emotional conditions may lead to sexual underdevelopment, and vice versa, will be admitted by most psychiatrists. Psychic and emotional states suspected of being neuroses and

occasionally leading to *nervous breakdown* may be associated with endocrine allergy. Depression is a relatively common symptom. The often bizarre nature of the syndrome leads physicians and others to suggest that the symptoms are not real. Anxiety and frustration are thus increased. Case 6 is an example. Emotional states may augment the allergy, as shown in the cases previously reported in which recurrent reactions occurred weeks after positive skin tests coincident with emotional upsets (Cases 2 and 12 in the earlier study[1]). The allergy may become manifest after long-continued or repeated emotional states. The studies of Donovan[14] and of Duncan and Taylor[15] favor such a mechanism. Psychic forces may directly cause any of the symptoms, as in hysterical conversion.

TABLE VIII. COMPARISON OF FREQUENTLY OCCURRING SYMPTOMS

	NUMBER OF CASES	PELVIC PAIN, %	PAINFUL BREASTS, %	BLOATING, %	NAUSEA, %	DIZZINESS, %	FATIGUE, %	IRRITABILITY, %	HEADACHE, %	HOT FLASHES, %	DEPRESSION, %	TENSION, %	ACNE, %
Premenstrual distress	67	52	66	55	41	22	44	28	29	38	15	35	12
Climacteric	66	23	30	17	36	33	50	12	48	61	18	9	3
Ovarian pain syndrome	60	100	50	33	44	38	42	18	37	19	3	10	7
Painful breasts and chronic cystic mastitis	24	43	100	17	25	21	38	25	25	21	4	0	13
Endometriosis	6	100	33	33	50	33	33	0	33	17	0	17	0
Headache	9	22	67	33	11	11	55	44	100	44	11	22	0
Hypogonadism	11	64	64	45	45	45	36	27	45	18	9	9	27

Most of the menstrual disorders, that is, abnormalities of bleeding, associated with these conditions are probably the direct result of ovarian failure, but some menstrual aberrations may result from the allergy. Midcycle bleeding occurs at a time when exacerbation of symptoms is common and it has long been observed in association with mittelschmerz. Both midcycle and premenstrual spotting have frequently been noted to disappear promptly after beginning treatment with pregnandiol and they have occasionally made their appearance with overdosage. Return to normal of both scanty and profuse menstruation, notably the former, has been observed with treatment. The menopause itself is the direct result of ovarian failure. Indeed, in most cases where symptoms are troublesome they occur long before the cessation of menstruation.

The intercyclic symptoms of endometriosis are often indistinguishable from those of the ovarian pain syndrome (Table VIII). (Pain during menstruation, dysmenorrhea, may occur with either, but it is probably not directly related to the allergy.) The similarity of response of patients with these two conditions to skin tests[1] and to treatment with pregnandiol (Tables IV, V, VI, and VII) suggests that patients with endometriosis and patients with the ovarian pain syndrome differ only in their reactions to steroid allergy.

It has been suggested that endocrine allergy might be the exciting factor in the metaplasia of cells of celomic origin which results in endometriosis.[1] According to the theory of celomic metaplasia, left-over embryonal cells of the celomic epithelium change into endometrial cells as a result of some unknown stimulus. Meigs[16] calls this unknown factor *abnormal physiology*. It is possible that this factor is the allergic response of the pelvic organs to steroids produced by the ovary, chiefly pregnandiol. The abnormal physiology seems to be manifested at least in part by hyperemia and congestion. Since endometriosis may occur without any symptoms whatever, it is probable that there are other mechanisms of its production.

CASE 10 (No. 1754).—A 34-year-old woman, para i, had an endometrioma, a small tumor produced by endometriosis, removed from the right inguinal canal shortly after the birth of her child four years before. She complained of pain in both lower quadrants, intermittent pain and tenderness in the left breast, dizziness, and fatigue. She had been trying for six months to become pregnant again. There was great tenderness on pelvic examination and slight nodular induration was noted in the cul-de-sac. Her symptoms disappeared while taking 1.0 mg. of pregnandiol daily by mouth. Six weeks later pelvic tenderness was notably less and the induration was not detected. Six months later she became pregnant. Following normal delivery, pelvic examination has been negative, but the existence of endometriosis has been proved by removal of another endometrioma from the right inguinal canal.

Many patients, particularly those in the categories of premenstrual distress and ovarian pain, date their symptoms from a pregnancy. Since steroids in the body fluids, notably pregnandiol, reach levels many times higher than those occurring at any other time, it is possible that sensitization occurs during pregnancy. Genetic or early environmental factors may be important. Endocrine allergy has been observed several times in sisters and in daughters and mothers.

There is a group of young patients, not included in the present study, whose symptoms of fatigue, nausea, and vertigo follow pregnancy and are not typical enough to be placed in any of the categories (Case 4). It is usually felt that these women are merely overworked and overtired in their burdensome, often new situation. It had long been noted, however, that they may be benefited by estrogen, and in most of those in whom it has been used pregnandiol has been remarkably helpful. These patients may be suffering from an acute allergy perhaps produced by pregnancy and augmented by the postpartum ovarian insufficiency. Large amounts of steroid substances are present in the body fluids during pregnancy, but for some time after delivery the condition seems to be reversed. Assay may reveal as much as 100 mg. of pregnandiol excreted in the urine in 24 hours during pregnancy. Shortly after delivery none can be detected.[17, 18*] Pelvic organs may have the clinical appearance of atrophy following parturition, and the condition is prolonged by lactation. Early menstrual cycles post partum are anovulatory.[19]

In all allergy the role of the autonomic nervous system, although not understood, seems to be of fundamental importance. The arrows in the chart

*The steroid is excreted as sodium pregnandiol glucuronidate. An interesting speculation is that failure of conjugation with glucuronide may be a cause of allergic reactions to pregnandiol.

might represent functions of the autonomic nervous system. A relationship to other allergies seems probable. About half of the patients give evidence of allergies to foods, pollens, etc.[1] Two cases of allergic rhinitis have been seen which were aggravated premenstrually. Both were greatly improved by pregnandiol, administered orally in one case and subcutaneously in the other. It has long been recognized that many allergic women experience aggravation of their symptoms premenstrually. Phillips[20] noted relief of both premenstrual distress and symptoms of recognized allergic disease such as asthma in patients hyposensitized with Synapoidin, a combination of urinary chorionic gonadotropin and extract of anterior pituitary gland.

It is possible that endogenous hormones and related substances other than the steroids also may evoke allergic reactions.[6, 20] Except for the steroids and chorionic gonadotropin, however, the same chemical compounds that occur in man are not available for treatment or study, and steroids are produced whenever a gonadotropic substance is given. Indeed, it is possible that the pregnandiol resulting from the luteinizing action of chorionic gonadotropin accounts for the reported beneficial effect of the chorionic hormone, A.P.L., in chronic cystic mastitis.[21]

Other Conditions in Which Endocrine Allergy May Be Involved

Dermatoses with exacerbation around the time of menstruation are listed in Table IV. One of these was a case of recurrent hives which was greatly benefited by pregnandiol given orally. Two cases of eczema, one in the climacteric and the other postmenopausal, were made worse by pregnandiol. Doses were too great. The patients did not return for further trials. All five cases of acne were benefited and this condition usually improved where it was an incidental symptom. It was frequently aggravated by too large doses (Case 8).

Five women classed as infertile achieved pregnancy during treatment with pregnandiol. Duration of infertility ranged from two to ten years. All were entirely normal except for symptoms of endocrine allergy as here described. There was one case of the ovarian pain syndrome. Four patients had symptoms of only mild premenstrual distress. All had relief of symptoms during treatment.

Other conditions in which skin sensitivity to pregnandiol has been observed and in which hyposensitization seems to have been beneficial are multiple sclerosis, arthritis, blepharitis, and central serous retinitis.* In most of these cases the occurrence of symptoms had some relationship to the menstrual cycle.

Summary and Conclusions

The hypothesis that many disorders related to ovarian function are caused by endogenous allergy to steroid hormones is supported by the results of treatment with pregnandiol. These disorders include premenstrual distress (ten-

*Cases of multiple sclerosis, retinitis, and blepharitis relieved during hyposensitization with progesterone, estrone, and estradiol, respectively, were previously reported. The steroid used was the one to which the patients showed the greatest skin sensitivity.[1]

sion), menopausal symptoms, the ovarian pain syndrome (congestion-fibrosis syndrome, pelvic hyperemic syndrome), painful breasts and chronic cystic mastitis, certain cases of endometriosis and hypogonadism, and headache and dermatoses associated with the menstrual cycle. A majority of patients with these disorders were shown in a previous study to be sensitive to pregnandiol, a metabolic product of progesterone, which has no known biological activity in man.

When pregnandiol was used therapeutically without regard to specific sensitivity, as one might use timothy pollen for hyposensitization for all sufferers from grass pollinosis in the northeastern United States, its over-all success was 76 per cent.

Pregnandiol is beneficial when given by mouth. It compares favorably with estrogen in the oral treatment of menopausal symptoms.

The subcutaneous route of administration is the more effective. Sixty-seven per cent of failures by the oral route were relieved by suitably small doses under the skin three or more times weekly. The over-all success of subcutaneous hyposensitization was 84 per cent.

More important than relief of symptoms in support of the hypothesis was the production by the steroid in larger doses of the same symptoms from which the patients were seeking relief. These *systemic reactions* were produced by both oral and subcutaneous administration.

A hypothesis correlating the various conditions associated with endocrine allergy is presented.

Materials and preparations which made this study possible were generously supplied by Parke, Davis & Company and by Ciba Pharmaceutical Products, Inc. I am also indebted to Dr. Leonard Horn, Dr. Jerome Glaser, and Dr. Leonard Axelrod for encouragement and help.

References

1. Heckel, G. P.: Surg., Gynec. & Obst. **92**: 191, 1951.
2. Heckel, G. P.: Surg., Gynec. & Obst. **86**: 260, 1948.
3. Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **57**: 211 and 637, 1949.
4. Theobald, G. W.: J. Obst. & Gynaec. Brit. Emp. **58**: 733, 1951.
5. Heckel, G. P.: J. Clin. Endocrinol. **11**: 790, 1951 (abstract).
6. Zondek, B., and Bromberg, Y. M.: J. Obst. & Gynaec. Brit. Emp. **54**: 1, 1947.
7. Kupperman, H. S.: Tace Symposium, The Wm. S. Merrill Co., 1952.
8. Rackemann, F. M.: J. Allergy **18**: 164, 1947.
9. Glass, S. J., and Rosenbaum, G.: J. Clin. Endocrinol. **3**: 95, 1943.
10. Van Wyck, H. B.: Address, Anglo American Humor, Interurban Obst. & Gyn. Soc., 1951.
11. Hansen-Pruss, O. C., and Raymond, R.: J. Clin. Endocrinol. **2**: 161, 1942.
12. Hansen-Pruss, O. C., and Raymond, R.: J. Clin. Endocrinol. **3**: 81, 1943.
13. Reynolds, S. R. M., Kaminester, S., Foster, F. I., and Schloss, S.: Surg., Gynec. & Obst. **73**: 206, 1941.
14. Donovan, J. C.: Am. J. Obst. & Gynec. **62**: 1281, 1951.
15. Duncan, C. H., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **64**: 1, 1952.
16. Meigs, J. V.: Ann. Surg. **127**: 795, 1948.
17. Browne, J. S. L., Henry, J. S., and Venning, E. H.: Am. J. Obst. & Gynec. **38**: 927, 1939.
18. Heckel, G. P.: New York State J. Med. **42**: 2103, 1942.
19. Sharman, A.: Fertil. & Steril. **2**: 371, 1951.
20. Phillips, E. W.: Ann. Int. Med. **30**: 364, 1949.
21. Morton, J. H.: J. Clin. Endocrinol. **6**: 802, 1946.

TOLUIDINE BLUE—AN EVALUATION IN THE TREATMENT OF UTERINE BLEEDING

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TOLUIDINE blue has been found to counteract the bleeding tendency in some bleeding states. The drug has an antiheparin-like action. In 1945 it was reported that there was an inhibitor to coagulation of blood in certain animals which had been subjected to prolonged irradiation.[1] It was further observed that toluidine blue injected intravenously neutralized this inhibitor and reversed the bleeding tendency.

Since that time the drug has been employed in a wide variety of hemorrhagic states.[2-8] However, a hemostatic effect has been observed only in those bleeding states associated with disturbance of the blood-clotting mechanism secondary to the presence of a heparin-like anticoagulator.

Until recently the drug was administered only by the intravenous route. The dose was determined on the basis of milligrams per kilogram of body weight. No serious side effects were reported from the intravenous administration of toluidine blue to man though certain disturbing side effects were noted. Nausea and vomiting have been reported.[9] Vertigo, hyperhidrosis, and mental excitation have been noted occasionally. Nystagmus and paresthesia of the face and extremities have been seen. The most common complaint is bladder irritability.[9] The drug appears in the urine as well as in other body fluids. In therapeutic dosage the urine becomes a pale blue green in color and at this point the patient often complains of tenesmus. One case of hemorrhagic cystitis followed the administration of toluidine blue but the relationship was probably coincidental.

Pharmacology

Normal animals which are injected for eight days with 5 mg. of toluidine blue per kilogram show no change in the coagulation time or capillary fragility. A one-plus urobilinogen in the urine is occasionally seen. No pathological changes can be found in the organs of the animals studied at autopsy.[10]

The minimal lethal dose has been determined at approximately 40 mg. per kilogram. Toluidine blue in normal animals has no effect upon the platelet count nor does it alter capillary permeability. Likewise it does not change the blood coagulation time in normal animals. Its effect seems to be solely that of hastening blood coagulation where there is excess of a heparin-like factor. It is only in the presence of an increased heparin-like factor in the blood as determined by protamine titration that toluidine blue blocks the bleeding diathesis.[11]

Bleeding from mucous membranes in patients with leukemia and secondary thrombocytopenic purpura with elevation of protamine titration has been

controlled with toluidine blue. Bleeding from mucous membranes in man following spray x-ray is associated with high protamine titration and has been controlled with toluidine blue.[1]

Protamine Titration.—

To determine the excess heparin-like factor in the blood, a back titration test against heparin with protamine sulfate has been devised. It is known that there are wide variations in tolerance of blood for added heparin in certain diseases. Normal blood tolerates heparin in a consistent manner. To test the tolerance an excess of heparin is added to a blood sample and back titrated with an antiheparin substance (protamine sulfate) to a clotting point. The technique employed is described.[10]

1. Reagents and Equipment:

(a) Protamine sulfate stock solution: 50 mg. of *powdered* protamine sulfate (Lilly) is dissolved in distilled water and made up to 50 ml. in a volumetric flask. *Do not use for twenty-four hours.* Keep refrigerated at 1 to 4° C. (it is stable for one week).

(b) Liquid commercial heparin (Abbott).

(c) Ten serology tubes (1 cm. inside diameter by 8 cm. long).

(d) Conical centrifuge tube, graduated to 15 ml.

(e) 10 ml. pipette, graduated to tip.

(f) 20 ml. syringe, glass tipped, with thin coating of light mineral oil.

(g) 18 gauge needles, 1½ in. long. These must be sharp and should be cleansed with a laboratory detergent and checked with hydrogen peroxide for evidence of peroxidase before drying with alcohol and ether.

All glassware must be chemically clean and dry before using.

2. Procedure:

(a) Pipetting the protamine solution: to each of the ten serology tubes the protamine sulfate solution is added from a micropipette in increments of 0.02 ml. (0.02 mg.) beginning with 0.02 ml. (0.02 mg.) in the first tube and ending with 0.20 ml. (0.20 mg.) in the tenth tube. The entire ten-tube range runs serially from 0.02 ml. to 0.20 ml. (0.02 mg. to 0.20 mg.).

(b) Pipette heparin into the conical tube: with a micropipette deliver 0.10 ml. (0.10 mg.) liquid commercial heparin to the bottom of the conical centrifuge tube.

(c) Venipuncture: cleanse skin with alcohol and dry. Apply tourniquet and make *clean* needle puncture. Gently aspirate (preferably by venous pressure) 12 ml. to 14 ml. of blood. If a good venipuncture is not accomplished on the initial puncture, another needle should be used as tissue juice or small amounts of blood may introduce serious error. The syringe should be free of air bubbles.

(d) Mixing the blood and heparin: remove needle from syringe and allow the blood to run gently down the side of the conical tube containing 1.0 mg. of heparin, bringing the blood to the 11 ml. mark. Stopper the tube with rubber stopper and slowly invert fifteen times to obtain reasonable mixing. The remainder of the test may be done in the laboratory and should be completed within one hour. If not pipetted at once, inversion mixing is repeated immediately before use.

(e) Pipetting the blood: the 10 ml. pipette is carefully filled with the heparinized blood mixture, avoiding aspiration of air bubbles. One ml. of blood is allowed to flow down the side of each of the ten tubes containing the protamine solution. Each tube is shaken briskly eight to ten times to obtain reasonable mixing of the heparinized blood with protamine solution. The entire series of tubes is then allowed to stand undisturbed for one hour at room temperature before the end point is read. The end point is defined in terms of the protamine content of the tube containing the least amount of protamine in which a solid clot has formed at this time.

(f) The end point: normally, the clot appears firm and retracts in all tubes containing 0.14 mg. of protamine or more and is entirely fluid in all the tubes containing 0.12 mg. or

less after one hour. Clot retraction, however, is slightly impaired in the tubes of high protamine concentration. The effect of moderate blood deficiencies confusing the end point is minimized by reading at one hour. This is especially true of thrombocytopenia and prothrombin deficiency. In women the end point may be increased during the menstrual period.

Clinical Study: Toluidine Blue and Its Effect on Uterine Bleeding

Evaluation of any hemostatic agent upon uterine bleeding presupposes an accurate definition of the type of uterine bleeding under discussion. When this study was undertaken it was presumed from previous observation that toluidine blue probably would affect only those uterine bleeding states associated with an abnormal protamine titration, that is, those cases in which the heparin-like factor in the blood was increased. In order to get an over-all picture, however, the compound was administered to patients with various types of uterine bleeding including normal menstruation. After some trial and error it was concluded that daily doses exceeding 250 mg. were frequently associated with marked bladder tenesmus which was the major side effect of which these patients complained. Experience revealed that 150 to 200 mg. of toluidine blue daily would reverse the protamine titration about as quickly and as satisfactorily as larger doses. During the latter part of the studies this was the dose employed on practically all patients.

The drug was given to patients starting three to eight days before the expected menstrual flow where the cycle could be predicted. Protamine titration was done on all patients before institution of therapy, in some patients while under medication, and in all patients during the bleeding episode that followed therapy.

The period of time required for reversal of the protamine titration, that is, for the toluidine blue to neutralize the heparin-like substance from the blood, was found to vary considerably.

The shortest period in which the titration was reversed was thirty-six hours; the longest period was in one patient who failed to have a reversal after ten days of medication and ten daily titrations, at the end of which time no further studies were made. That this patient was taking the medication was obvious from examination of her urine.

Normal Menstruation.—

Toluidine blue was administered in a dose of 200 mg. daily to six patients with normal cyclic menstruation. The average duration of flow in these patients was five days and the total blood loss in each cycle was estimated to be within normal limits. Protamine titration was negative in all of these patients. Following the administration of toluidine blue there was no change in the amount or duration of flow in any patient.

Cyclic Hypermenorrhea From a Proliferative-Phase Endometrium.—

Eight patients with a history of regular cyclic menstruation but in whom the chief complaint was excessive amount or prolonged duration were studied. The amount and duration of flow in each of these patients were such as to partially incapacitate them during each menstruation. In most of the cases it was necessary to wear additional protection on the first one to three days

of menstruation. Endometrial biopsies on all patients in this group were taken during the bleeding episode and all were found to be in the proliferative phase.

The drug was administered in a dose of 150 mg. daily to three patients and 200 mg. daily to five patients over a period varying from three to twenty days. The protamine titration in three of these patients before treatment was positive and in four, negative. In the three patients who had a positive protamine titration with reversal to normal during the treatment period there was a marked diminution in the amount of blood loss and duration of the flow. For this group it was estimated that the amount and duration of flow were reduced about fifty per cent. In the patients with negative protamine titration before treatment no reduction in flow occurred.

Cyclic Hypermenorrhea Associated With a Secretory-Phase Endometrium.—

There were fifteen patients in this group. The average duration of flow was 8½ days and the average estimated blood loss was at least twice the expected norm. Endometrial biopsy showed a secretory phase in five patients of this group. Three of the patients were known to have fibroid tumors and two of them were thought to have adenomyosis. The protamine titration was positive in nine of the fifteen patients.

Toluidine blue was given in a dose of 150 to 200 mg. daily over a period varying from two to five days before the expected menstruation. In eight of the patients with a positive protamine titration duration of flow averaged six days after treatment and the blood loss was reduced to normal. In the six patients with negative protamine titration no change in amount or duration of flow occurred.

Patients with a normal endocrine cycle, normal secretory-phase endometrium, and in the absence of organic pelvic disease who bleed profusely and over a period of time longer than normal and who have a positive protamine titration, are patients suited for toluidine blue therapy. It is the only group of patients in whom hemostasis can be expected to follow consistently in the wake of treatment.

Polymenorrhea.—

Thirteen patients with intermenstrual bleeding were studied. Endometrial biopsies were obtained on five of these patients and each of them had a proliferative-phase endometrium of atrophic, hyperplastic, or persistent type. Protamine titration was positive in four of these patients and negative in nine. Administration of the drug in a dose of 100 to 200 mg. daily over a period of three to sixteen days was followed by no significant change in the amount or duration of uterine bleeding. A regular cycle was not established. In two of the patients with positive protamine titration temporary control of bleeding was obtained when the drug was started but one of these patients lapsed back into her bleeding phase while still under treatment.

These patients with polymenorrhea and intermenstrual bleeding usually have some endocrinopathy in their backgrounds. The presence of a persistent proliferative-phase endometrium, or at best a transitional endometrium in

these patients would suggest corpus luteum failure. Where the bleeding is secondary to a disturbance in endometrial physiology resulting from a change in ovarian steroid production it appears that toluidine blue has no hemostatic effect even in those patients in whom the protamine titration is positive.

Conclusions

1. Toluidine blue administered orally is an effective uterine hemostatic in those cases of uterine bleeding related to an increased heparin-like factor in the circulating blood as determined by protamine titration.

2. Uterine bleeding secondary to endocrinologic disturbance, organic pelvic disease, or endometrial dysfunction is not influenced by toluidine blue.

3. Cyclic hypermenorrhea from a secretory-phase endometrium in patients with a positive protamine titration is controlled by this drug in a large percentage of cases.

4. Bladder tenesmus and frequency are often side effects of toluidine blue. Nausea and vomiting are occasionally seen. No other evidence of toxicity was observed in this group of patients.

References

1. Allen, J. G., and Jacobson, L. O.: Science **105**: 388, 1947.
2. Allen, J. G., Bogardus, G., Jacobson, L. O., and Spurr, C. L.: Ann. Int. Med. **27**: 382, 1947.
3. Allen, J. G., Jacobson, L. O., and Grossman, B. J.: J. Lab. & Clin. Med. **33**: 1480, 1948.
4. Holoubek, J. E., Hendrick, J. V., and Hollis, W. J.: J. A. M. A. **139**: 214, 1949.
5. Allen, J. G., and others: J. A. M. A. **139**: 1251, 1949.
6. Allen, J. G., and others: Surg., Gynec. & Obst. **89**: 692, 1949.
7. Allen, J. G., and others: J. Lab. & Clin. Med. **34**: 473, 1949.
8. Elghammer, R. M., and others: Surg., Gynec. & Obst. **89**: 764, 1949.
9. Lathrop, Clarence A., Dieckmann, W. J., and Allen, J. G.: Am. J. Obst. & Gynec. **59**: 897, 1950.
10. Abbott Laboratories, Research Division: Personal communication.
11. Rumbolz, W. L., Moon, C. F., and Novelli, J. C.: Am. J. Obst. & Gynec. **63**: 1029, 1952.

MENORRHAGIA—TREATMENT WITH INTRAVENOUS ESTRADIOL*

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MENORRHAGIA has long been one of the difficult problems confronting the physician. Hematinics, hormones, curettage, radium, and hysterectomy have all been given a place in the treatment of menorrhagia. Curettage is generally of only temporary value, insertion of radium is being done less frequently, and hysterectomy is a major procedure, which may be performed only during or near the menopause.

Until recently the hormones also have not proved of great value in treating menorrhagia. Anterior pituitary extract, the androgens, and progesterone have all been used, but the results have not been encouraging, particularly when the extent of bleeding is considerable.

Rakoff[1] has stated that the practice of administering huge doses of estrogens by mouth or by intramuscular injection with the aim of producing sudden cessation of bleeding not infrequently has given rise to further bouts of hemorrhage even though a favorable initial response is sometimes obtained.

Hamblen's[2] observations were that most functional uterine hemorrhages result from critical teetering of estrogen levels and failure of the normal midmenstrual rise to check bleeding by initiating another wave of endometrial growth. If this thesis be true, episodes of bleeding can be stopped by raising estrogen levels by estrogen therapy. As a rule, however, it takes several days to secure "estrogen hemostasis." Hamblen gave estrogen therapy orally, preferring natural estrogens in general and particularly when functional uterine hemorrhage was treated. Usually hemostasis was produced within three to five days.

Bickers[3] has said that patients bleeding from an endometrium in the proliferative phase are candidates for treatment by endocrine therapy. Bleeding can be controlled satisfactorily by the administration of large oral doses of estrogens. Twelve patients suffering from anovulatory metrorrhagia all of whom were partially exsanguinated from prolonged and excessive bleeding were treated with estinyl estradiol, 0.3 mg. daily for 20 days. Uterine bleeding ceased in all cases except one within 6 days after starting treatment.

Ross and Gill[4] treated more than 200 cases of excessive functional bleeding. Bleeding was controlled satisfactorily in 99 per cent by the injection of stilbestrol in oil (25 mg. per cubic centimeter) into the anterior lip of the cervix uteri.

Patients whose cycles were of normal length but whose bleeding was profuse and continued up to 8 days were treated by Smith[5] with stilbestrol in 5 mg., 10 mg., and 25 mg. doses daily for 25 days, or with estrone sulfate, 10 mg. daily

*We wish to thank the Schering Corporation of Bloomfield, N. J., for the generous supply of Progynon in propylene glycol, which has made this study possible.

for 25 days. The occurrence of bleeding between the sixth day and the end of estrogen treatment indicated the presence of some undiagnosed condition within the uterus.

According to Greenblatt and Barfield,[6] acute uterine bleeding is generally arrested in a few hours by intravenous injection of estrogen. A natural equine product such as estrone sulfate may be given three or four times, in doses of 5 c.c. or 20 mg., every 6 to 12 hours. After the initial arrest of bleeding, oral estrogen in decreasing dosage prevents withdrawal bleeding. Cyclic progesterone therapy is given each month until spontaneous ovulation is resumed. The therapy may be successfully used for patients with functional uterine bleeding, but care must be exercised because apparently good, though temporary, results are also obtained in cases of hemorrhage from cancer or ectopic pregnancy.

We have treated 15 cases of menorrhagia with estradiol in propylene glycol intravenously. The several cases listed below illustrate the clinical situations in which it may be employed, the manner of administration, and the results that may occur.

O. B., aged 32 years, para ii, was seen on Nov. 29, 1951, because of menorrhagia. The patient had been bleeding since September 4. Estradiol in propylene glycol, 10,000 R.U., was administered intravenously. The bleeding stopped within 48 hours. The patient had a period on January 15 for three days, then bled off and on from February 2 to February 16. Extradiol in propylene glycol was again administered intravenously with cessation of bleeding within 48 hours. The patient had a moderate period from February 24 to 26. Physical examination of this patient was negative, and there was no history or any evidence of pelvic abnormality.

C. P., aged 27 years, para iii, gravida iv, suffered a miscarriage at two months in April, 1950. She later consulted us because of menorrhagia lasting from June 25 to July 19, and from September 15 to October 1. At that time she was given testosterone propionate, in two successive 25 mg. injections but continued to bleed until October 11. On that date, estradiol in propylene glycol was given intravenously in a dose of 10,000 R.U. daily for two days. The patient stopped bleeding completely within 24 hours after the second injection. The periods have subsequently been regular and the patient has conceived and was delivered normally.

J. G., aged 11 years, was referred to us because of vaginal bleeding of seven weeks' duration, beginning with her first menstrual period. Her height, weight, and general physical examination were normal, but the rectal examination revealed an almost infantile development of the cervix and uterus. Estradiol in propylene glycol, 20,000 R.U., was administered intravenously. There was a considerable decrease in the flow after the first injection. The patient was given a second and third injection daily and bleeding ceased completely after the third injection. A fourth injection was given two days after the third. No withdrawal bleeding took place, though 80,000 R.U. of estradiol in propylene glycol had been given. The referring physician has told us that this patient has menstruated regularly since, with a moderate flow.

F. U., aged 16 years, was seen in consultation because of menorrhagia on Jan. 27, 1950. A curettage had been advised by another physician. Menstruation began at 11½ years, occurred every 2 to 3 months, lasted eight days, and was very heavy. The last menstrual period began on January 10 with hemorrhage the first three days, and lasted eight days altogether. Bleeding began again on January 22, continuing to the time the patient visited us. The general and vaginal examinations were negative. The basal metabolic rate taken in 1949 had been minus 19. Estradiol in propylene glycol, 20,000 R.U., was given intravenously.

Bleeding stopped in less than 24 hours. The basal metabolic rate taken soon after was minus 7. The patient's periods have been regulated with cyclic therapy and no medication has been given since 1951.

Summary and Comments

1. Menorrhagia can be successfully treated by the administration of Progynon in propylene glycol intravenously.

2. Progynon in propylene glycol intravenously is of considerable value in treatment of any functional *acute* uterine bleeding.

3. There were no reactions of any kind in this series.

4. Menopausal bleeding should *not* be treated with hormones.

References

1. Rakoff, A. E.: M. Clin. North America **32**: 1509, 1948.
2. Hamblen, E. C.: M. Clin. North America **32**: 57, 1948.
3. Bickers, William: AM. J. OBST. & GYNEC. **51**: 100, 1946.
4. Ross, J. W., and Gill, C. M.: AM. J. OBST. & GYNEC. **56**: 723, 1948.
5. Smith, G. Van S.: New England J. Med. **241**: 410, 1949.
6. Greenblatt, R. B., and Barfield, W. E.: J. Clin. Endocrinol. **11**: 821, 1951.

THE DIAGNOSTIC ACCURACY OF THE ENDOMETRIAL ASPIRATION SMEAR

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BECAUSE of its impressive record of diagnostic accuracy in early cancer of the cervix and in carcinoma in situ, the vaginal and cervical smear technique has won widespread scientific recognition.[1-5] In medical practice, its simplicity, inexpensiveness, and painlessness mark it as a thoroughly practicable office procedure.[1, 2]

Vaginal and cervical spreads, however, have made a relatively poor showing in the diagnosis of endometrial carcinoma.[6, 7, 8] In order to improve this poor cytologic showing, and perfect a method equally simple, equally convenient, one that would spare the patient the hazards of repeated anesthesia and operation, and the expense of hospitalization, the endometrial aspiration smear was developed.[8]

Table I. Comparative Accuracy in Diagnosis of Endometrial Pathology Utilizing Cervical, Vaginal, and Endometrial Smears

Total Cases 125—100%
Symptoms and Pathology 86—68.80%

	TOTAL NO. PROVED HISTORY		CERVICAL AND VAGINAL SMEARS						ENDOMETRIAL SMEARS					
			ACCURACY		FALSE NEG.		FALSE POS.		ACCURACY		FALSE NEG.		FALSE POS.	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Adenocarcinoma of endometrium	16	12.80	10	62.50	6	37.50	1	0.80	16	100	0	0	0	0
Endometrial hyperplasia	18	14.40												
and			9	34.61	17	65.39	2	1.60	19	73.07	7	26.93	3	2.40
Endometrial polyps	8	6.40												
	26	20.80												
Luteal phase of endometrium*	23	18.40	18	78.26	5	21.74	2	1.60	14	60.87	9	39.13	4	3.20

*Secretory late interval.

In May, 1952, 125 cases were reported in which the endometrial smear was successfully utilized at University Hospital of New York University-Bellevue Medical Center (Table I).[8] In this study, 16 cases of endometrial carcinoma were discovered, 6 of which had been missed by the vaginal and cervical smears. Since that time, more than 1,000 new cases have been studied in which the endometrial smear technique was applied. Although final analytic figures are not yet available for this work, the results are emphatically good.

Description of Method

The method and material employed are as follows: After vaginal and cervical smears have been taken, the cervix and endocervical canal are painted with Tincture of Merthiolate and a uterine cannula is introduced into the endometrial cavity. The cannula has a beveled edge, is malleable, and is thin enough to pass through the internal cervical os without too much difficulty (Fig. 1). In the event that some difficulty is encountered, a tenaculum is placed on the anterior lip of the cervix. When the cannula is introduced into the endometrial cavity, a 5 or 10 c.c. syringe is attached to the cannula, and gentle suction is applied. The cannula is then removed, and the aspirated material is expressed on a slide by forcing air through the cannula with a syringe. The expressed material is then spread on slides and immediately immersed in fixative. For proper staining, our procedure consists of staining the nucleus with Harris' hematoxylin and counterstaining the cytoplasm with OG6 and EA36 or EA50, to insure a light and transparent coloration of the cytoplasm. A very deep staining of the nucleus should be avoided since it may give a false impression of hyperchromatism.

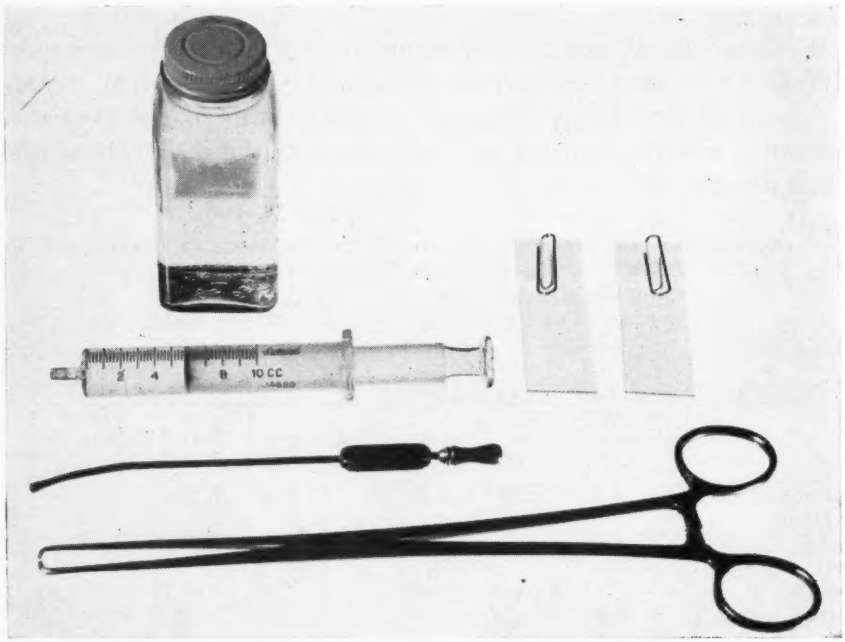

Fig. 1.—The material employed for obtaining endometrium for an aspiration smear, showing the thin malleable cannula which is introduced into the endometrial cavity.

Results

To date, two significant findings have emerged. One: the endometrial smear reliably detects carcinoma in this area when vaginal and cervical smears fail.[8] It does so because it affords a fresh, well-preserved, dependable sampling of endometrial cells. This is in contrast to vaginal and cervical spreads, in which the endometrial cells are often degenerated, and thus obscure the diagnostic picture. Furthermore, since some degree of stenosis is commonly found in postmenopausal women, the number of desquamated endo-

metrial cells may be limited on vaginal and cervical smears obtained from such patients. As another advantage, the confusing presence of endocervical cells is eliminated from the endometrial smear.

The second significant finding is predicated on certain limitations frequently encountered in endometrial biopsy and diagnostic curettage. These limitations we all know: uterine material taken from the postmenopausal patient is often too scanty for accurate evaluation; in these cases, the pathologic report will read "Insufficient material." Or the report may be inconclusive because material has been lost in the paraffin block. The endometrial aspiration smear is particularly advantageous when these two time-honored diagnostic methods are thus hamstrung. The scantiest uterine material produces an abundant, even sampling of exfoliated cells for cytologic study, when the endometrial smear technique is utilized.

The criteria for the diagnosis of endometrial carcinoma which have been established after 3 years of evaluation have proved to be gratifyingly accurate.[1] In fact, it has been found that, when these criteria are satisfied—and subsequent curettage was negative—the specimen, when eventually removed, harbored a carcinoma.

The three cases herein discussed belong to this category. Cytologic examinations were positive. Curettage and biopsies were negative, or produced insufficient material for diagnosis. On removal of the specimen, carcinoma was found.*

CASE 1.—A. S., a 58-year-old white woman, moderately obese, was admitted to Bellevue Hospital on Feb. 7, 1952, complaining of postmenopausal bleeding of 3 years' duration, recurring every 2 or 3 weeks, bright red, with clots. Menopause had occurred 13 years earlier. For 8 weeks preceding admission to the hospital, vaginal bleeding measured about 1 teaspoonful following bowel movements.

No abdominal masses were palpable on physical examination. Pelvic examination revealed a parous introitus with a second-degree cystocele and a third-degree rectocele. The cervix pointed posteriorly and was moderately firm. The os was closed, freely movable, and nontender. No adnexal masses were palpable. On speculum examination, the cervix appeared irregular, scarred, with a blanched area on the anterior lip that bled easily. The impression on admission was (1) suspicious for carcinoma, (2) postmenopausal bleeding.

The laboratory work was noncontributory. Vaginal and cervical smears taken Feb. 9, 1952, were reported negative. The aspiration smear from the endocervical canal and corpus was positive for adenocarcinoma (Fig. 2).

A diagnostic curettage was performed on Feb. 19, 1952, and 4 quadrant biopsies were taken. The cervical biopsies showed subacute cervicitis. The curettings were very scanty and insufficient for diagnosis. The patient was discharged on March 4 with a diagnosis of chronic cervicitis and postmenopausal bleeding. She was readmitted on April 2, approximately 4 weeks later, because of continued bleeding. The physical findings were the same as on the first admission. Speculum examination revealed the anterior cervix to be eroded and bleeding on touch.

The impression was (1) postmenopausal bleeding with probable early malignancy of the cervix or corpus; (2) cystocele and first-degree prolapse. On April 4, 1952, despite negative curettings, a vaginal hysterectomy and anterior colporrhaphy were performed.

*Since this report, 5 additional cases have been encountered in which the endometrial smear aided us in making a correct diagnosis of carcinoma when biopsy and curettage were inconclusive.

Macroscopic examination of the specimen revealed a normal uterus. The endometrial cavity was uniform and lined with a thin hemorrhagic endometrium. The cervix measured 2.5 cm. in length. The portio showed signs of recent surgical trauma and mild inflammation with erosion. Grossly, the endocervix appeared normal.

Microscopic sections of the cervix revealed marginal layers of squamous epithelium, which were uniform except for areas of fragmentation and hemorrhage. One section (Cx.-8) showed an area in which there was marked irregularity and hyperplasia of the glands of the endocervix. These glands were filled with thick layers of cuboidal and low-columnar type cells, showing marked pleomorphism and hyperchromatism (Fig. 3). Frequent multinucleated cells were seen. Sections of the corpus revealed a thin marginal endometrium, grossly atrophic in appearance, with irregular glands lined by columnar cells.

The diagnosis was early carcinoma of the cervix, atrophic endometrium with slight adenomyosis, and fibromyoma uteri.

The patient ran an uneventful postoperative course and was discharged on the tenth postoperative day.

To summarize, the vaginal and cervical smears were negative, the endometrial smear was positive. The uterine curettings were insufficient for diagnosis. The cervical biopsies were negative. The final diagnosis on the operative specimen was carcinoma of the cervix. The carcinoma was at the junction of the internal os and the endometrial cavity, which would explain why vaginal-cervical smears were deficient in detecting the lesion. Material for the endometrial smear was undoubtedly aspirated from the endocervical canal, adjacent to the endometrial cavity.

CASE 2.—R. C., a 70-year-old obese woman, was first seen in the Gynecologic Out-Patient Department of University Hospital on April 18, 1950. She complained of vaginal staining of one year's duration. Menopause had occurred at the age of 35. Pelvic examination revealed a mild cystocele and rectocele, uterus anterior, normal in size, and freely movable. No adnexal masses were palpable. The cervix showed no signs of erosion.

The diagnosis was (1) postmenopausal bleeding, (2) mild cystocele and rectocele. Vaginal and cervical smears taken on April 18, 1950, showed an atrophic menopausal pattern with some anisocytosis of the nuclei and hyperchromatism. The impression was (1) atrophy due to menopause, (2) a few suspicious cells present which could not be classified as malignant. On May 16, 4 endometrial aspiration smears were taken. The diagnosis was positive for endometrial adenocarcinoma, and a diagnostic curettage was recommended (Fig. 4).

The patient continued to stain intermittently but did not appear in the clinic until a month later, at which time she was admitted to the hospital for a diagnostic curettage and biopsy of the cervix. Physical findings at that time duplicated the initial report. The laboratory findings were noncontributory.

Examination under anesthesia revealed a cervix slighly eroded on the anterior lip but otherwise normal: a finding confirmed by the pathologic examination. The eroded area did not bleed on touch. The uterus was enlarged to the size of a two months' gestation and a firm globular mass was palpable on the posterior wall. The adnexa were normal. The uterus was sounded to a depth of 4 inches, and yielded very scanty curettings. A diagnosis on the uterine curettings could not be made because of insufficient material. The cervical biopsy was negative. The patient was discharged on July 4, 1950. On May 23, 1951, endometrial aspiration smears taken in the outpatient department were positive for adenocarcinoma. Since the initial curettage had not proved helpful, the patient was readmitted on October 5 for another curettage. Endometrial smears taken at this time were again positive for malignancy. Curettings were obtained at this time, a diagnosis of adenocarcinoma was made, and the patient was treated with intracavitary radiation (Fig. 5).

Six weeks later, follow-up smears, vaginal, cervical, and endometrial, were positive for adenocarcinoma. The patient refused to undergo hysterectomy and has been lost to follow-up.

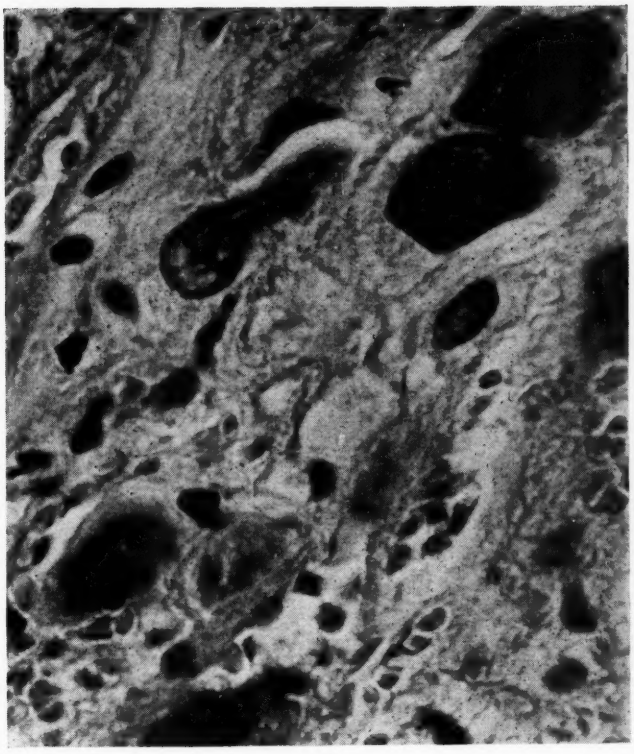

Fig. 2 (Case 1).—Aspiration smear from the endocervical canal showing malignant cells.

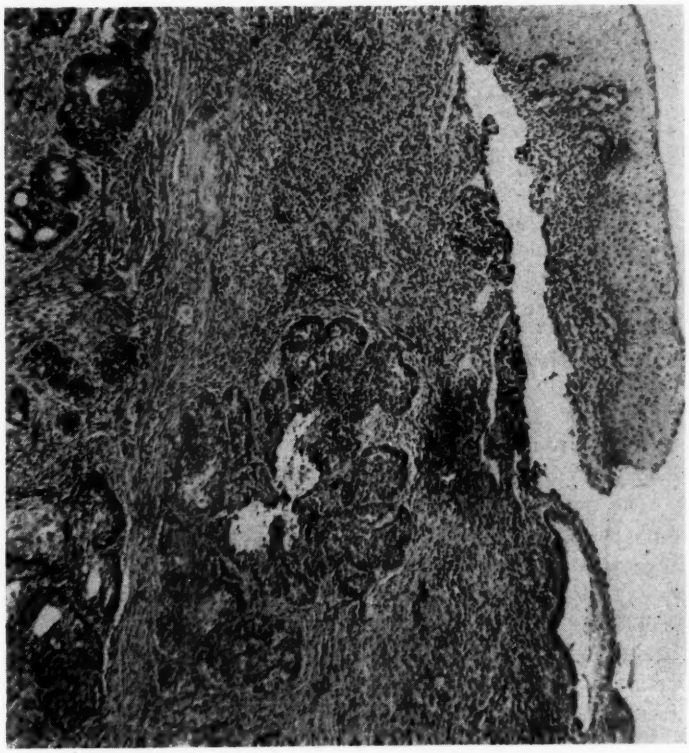

Fig. 3 (Case 1).—Histologic section of the endocervix showing irregularity and hyperplasia of the glands of the endocervix. The glands are filled with cells showing pleomorphism and hyperchromatism.

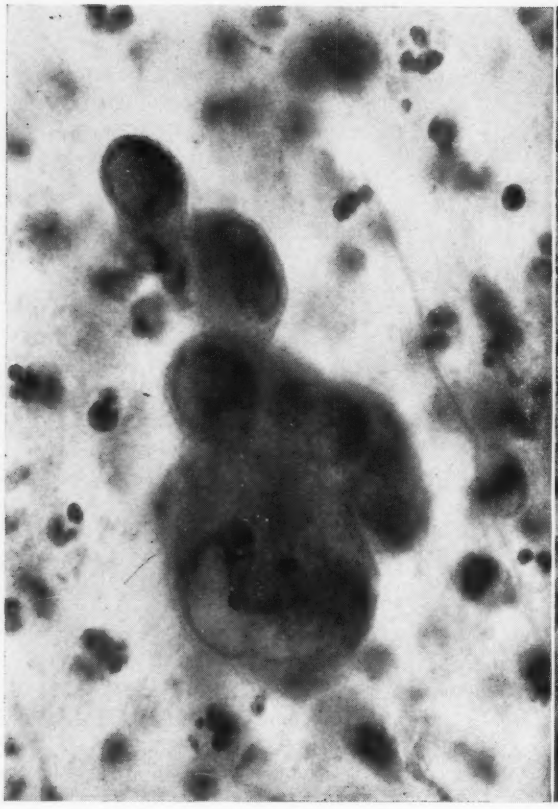

Fig. 4.

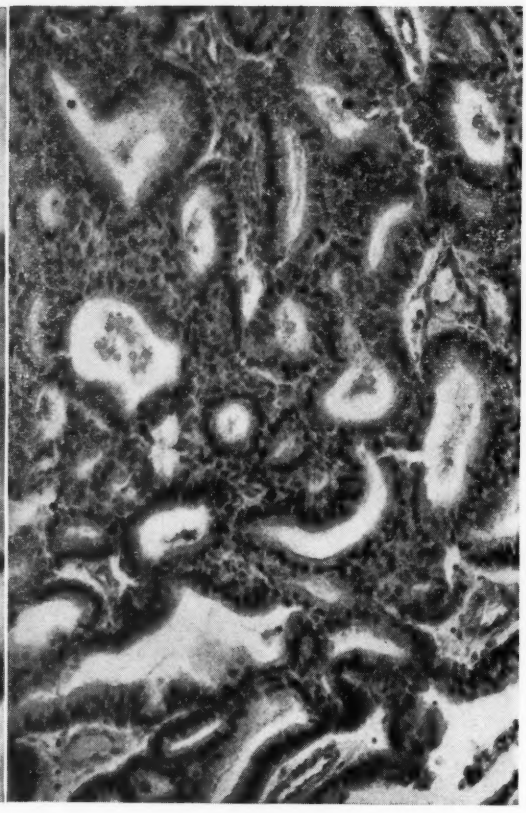

Fig. 5.

Fig. 4 (Case 2).—Endometrial aspiration smear showing well-differentiated adenocarcinoma cells.

Fig. 5 (Case 2).—Histologic section showing well-differentiated adenocarcinoma glands.

To summarize, the endometrial aspiration smear was positive. The first curettage was inconclusive because of insufficient material. Repeated smears were positive. The second curettage was positive, substantiating the cytologic diagnosis.

CASE 3.—E. G., a 62-year-old white woman, complained of vaginal bleeding. Sixteen years earlier, at the age of 46, she had a radiation menopause following treatment for a bleeding fibroid uterus. Shortly before being seen at University Hospital, the patient had been thoroughly examined, and at a reputable clinic physical and laboratory findings had all been within normal range. She continued to bleed, however, and a curettage had been performed. The report on the curettings read: no evidence of cancer. She then consulted a private physician, who took an endometrial aspiration smear in his office.* A diagnosis of undifferentiated adenocarcinoma was made at the Gynecologic-Cytology Laboratory of University Hospital (Fig. 6). This was confirmed by curettage (Fig. 7). On surgical removal of the uterus, cervix, tubes, and ovaries, the entire left cornua was found occupied by a fungating cauliflower mass extending halfway through the myometrium. There was no metastasis to the tubes or ovaries. The patient made an uneventful recovery, and was discharged on the tenth postoperative day.

*Acknowledgment is made to Dr. Locke L. Mackenzie for his kind permission to report this case.

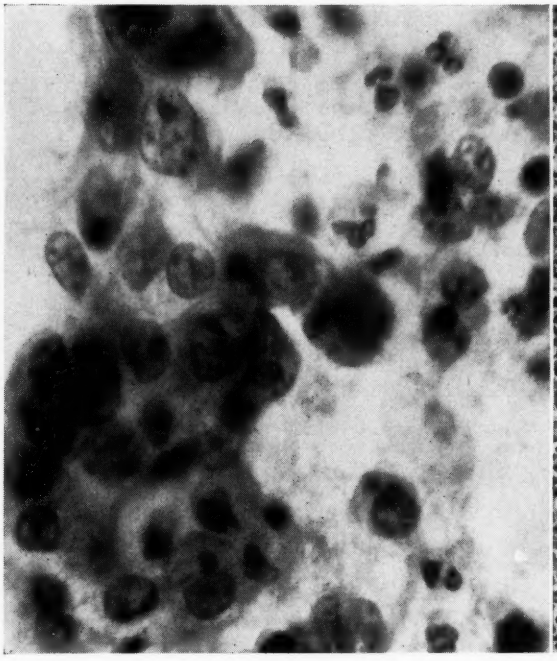

Fig. 6.

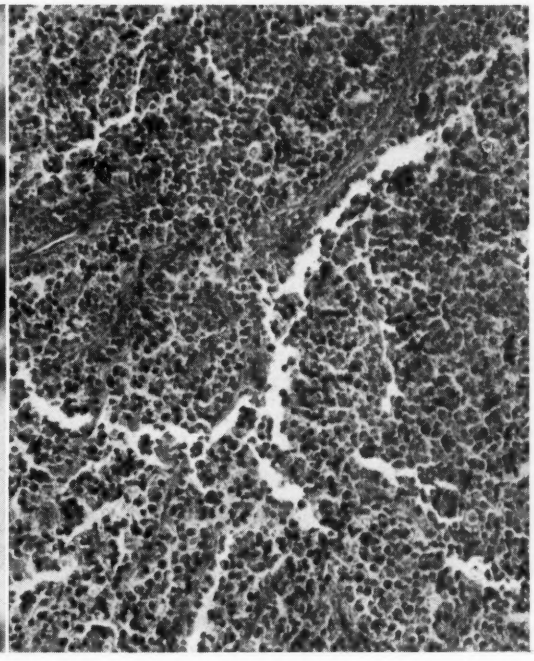

Fig. 7.

Fig. 6 (Case 3).—Endometrial aspiration smear showing undifferentiated adenocarcinoma cells.

Fig. 7 (Case 3).—Histologic section showing undifferentiated adenocarcinoma of the endometrium.

In this case, the initial curettage was negative. The patient continued to bleed. Endometrial smear was positive, substantiated on later curettage. On removal of the specimen, carcinoma of the endometrium was found.

Conclusions

1. Three cases have been reported wherein the endometrial smear indicated the presence of malignancy and in which the initial curettage or endometrial biopsy was negative or inconclusive. The cytologic diagnosis in two cases was substantiated later by histologic examination of the specimen, and, in one, by positive curettings obtained at a second curettage.

2. The endometrial aspiration smear is an important adjunct in gynecologic diagnosis, meriting inclusion in every gynecologic examination of the patient with postmenopausal bleeding or abnormal bleeding during the menarche.

References

1. Graham, R. M., Sturgis, S. H., and McGraw, J.: Am. J. Obst. & Gynec. **55**: 303, 1948.
2. Graham, R. M., and Meigs, J. V.: Am. J. Obst. & Gynec. **58**: 843, 1949.
3. Daro, A. F., Rubenstein, M. W., and Gallin, H.: Am. J. Obst. & Gynec. **65**: 364, 1953.
4. Douglas, G. W., and Studdiford, W. E.: Surg., Gynec. & Obst. **91**: 728, 1950.
5. Achenbach, R. R., Johnston, R. E., and Hertig, A. T.: Am. J. Obst. & Gynec. **61**: 385, 1951.
6. Burns, E. L., Hartung, W. H., Jr., and Brittingham, E.: Arch. Path. **50**: 699, 1950.
7. Hecht, E. L.: Am. J. Obst. & Gynec. **64**: 81, 1952.
8. Hecht, E. L.: New York State J. Med. **52**: 2745, 1952.

Department of Case Reports New Instruments, Etc.

A CASE REPORT OF CHOREA GRAVIDARUM COMPLICATING FIVE PREGNANCIES

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CHOREA gravidarum is a reportedly serious complication of pregnancy. The incidence is estimated at about one in 3,000 deliveries and the maternal mortality up to 15 per cent.[3] It occurs most frequently in primigravidas and may recur in subsequent pregnancies. The mortality of patients who had had chorea in childhood is less than half that of those who did not have the disease. In severe cases, those in whom the movements are so violent and continuous as to disturb rest, lead to exhaustion, and interfere with nutrition, the mortality is about 13 per cent.[2] The fetal mortality is reported as high as 50 to 70 per cent, including stillbirths and neonatal deaths (due mostly to prematurity). Many of the other surviving babies show abnormalities.[1]

McElin, Lovelady, and Woltman[4] in 1948 reviewed the recent literature and presented 5 cases from the Mayo Clinic records. Beresford and Graham[5] also presented a review of cases including several of their own. The outcome of these cases was reported as favorable for the mother and baby. These and other articles in the literature in the past revealed no cases of chorea gravidarum complicating several repeat pregnancies.

This is a report of a 27-year-old white woman who has had chorea gravidarum with five of her pregnancies and a favorable outcome of all. Six of her pregnancies terminated early in spontaneous abortions without evidence of chorea.

Past History.—The patient was 27 years old, gravida xi, para iv, at term on Jan. 20, 1952. She had four viable pregnancies prior to this one, each accompanied in the last trimester by purposeless involuntary movements of all limbs and facial grimacing. These seizures were not accompanied by incontinence, tongue biting, or unconsciousness. The pregnancies progressed uneventfully until the last four to six weeks, at which time she started to develop these involuntary movements. The movements became more violent after several days and this change was followed by the premature onset of labor. The labors were all of short duration, terminating with the delivery of living premature infants under 5 pounds, and all apparently in good condition.

Immediately after delivery the condition improved rapidly; after two to four weeks post partum there was no detectable sign of these seizures. The condition seems to have become progressively worse with each pregnancy. There has been no associated fever or infection. Between pregnancies the patient seems to do well, showing no signs of chorea. The children are all living and well.

The patient denies any history of rheumatic fever nor has she had frequent respiratory infections. She admits no history of nervous disorders or convulsions in childhood. There is no history of hypertension or albuminuria in the past. The husband denies any mental change after pregnancies.

Present Illness.—The patient was admitted at 10:50 P.M. on Dec. 23, 1951, at 36 weeks' gestation. At that time she was having violent purposeless choreiform movements of the arms and legs as well as marked facial grimacing. She was conscious and seemed to respond well to simple commands. She showed no tongue biting, frothing at the mouth, or incontinence.

The husband reported that about one month before, she attended the funeral of one of her relatives and then started having mild choreiform movements. These persisted off and on without incapacitating her until one week before admission, when the movements became much more violent and forced her to go to bed. She could not stand or feed herself. On the day of admission the patient could no longer be controlled at home and was brought to the hospital.

She had not been seen in our clinic during this pregnancy. She was reported to have had some prenatal care from an outside doctor, but her course was uneventful until the onset of these symptoms. Her husband denied any history of toxemic symptoms, fever, arthralgia, or respiratory infection.

Physical Examination.—The patient was a white woman having violent choreiform movements of the limbs and facial grimacing. She was conscious and able to react to simple commands. The temperature was 98.8° F. The systolic blood pressure was about 120 mm., being difficult to record exactly because of the movements.

The heart showed a Grade I systolic murmur. There was no apparent joint involvement. The height of the fundus measured 24 cm. She was having uterine contractions, every 5 to 8 minutes, lasting 30 to 45 seconds. The membranes were intact and there was no bleeding. Rectal examination revealed the cervix to be effaced and 1½ fingers dilated, the vertex presenting at the level of the spines. The fetal heart rate was 128 to 140 per minute.

Laboratory Results.—There was a trace of albumin, otherwise the urine was negative. The nonprotein nitrogen was 34 mg. per cent. The carbon dioxide combining power was 46 volumes per cent. Plasma uric acid was 6.2 mg. per cent. The erythrocyte count was 3.6 million, leukocytes 8,800 with polymorphonuclear cells 57 per cent, lymphocytes, 42 per cent, and eosinophils 1 per cent. The hemoglobin was 9.5 Gm.

The impression was: (1) Intrauterine pregnancy, about 36 weeks. (2) Chorea gravidarum. (3) Early labor.

Clinical Course.—The patient received heavy sedation with Sodium Amytal intravenously and intramuscularly and this medication stopped all movements. Uterine contractions continued and the fetal heart tones remained good.

At 1:10 A.M. on Dec. 24, 1951, the cervix became completely dilated and the head presented on the perineum. The choreiform movements returned as she recovered from her narcosis and seemed to be stimulated by second-stage labor pains. Under ether anesthesia, the membranes were ruptured artificially and this was followed by the spontaneous delivery of a premature female infant with a good cry and color. The third stage was completed without difficulty. The placenta was small and showed numerous healed infarcts. Immediately after delivery the patient was given more barbiturate sedation and fluids by clysis. A Foley catheter was inserted and penicillin started.

Sedation was continued with barbiturates and paraldehyde until Dec. 28, 1951, when it was decreased to an amount suitable for an ambulatory patient. Before this time it was noted that movements returned when sedation was not adequate. Her postpartum course was afrebrile and otherwise uneventful. The urinary output was normal and the slight albuminuria disappeared.

Neurologic consultation did not disclose any positive physical findings. Electroencephalogram did not reveal any cortical discharges; the conclusion was: chorea

gravidarum. The patient was able to walk on the fifth postpartum day and was discharged on the tenth postpartum day free of any symptoms. The baby, though small, did well and was discharged with the patient. Tubal ligation was advised but refused.

Summary

A report has been made of a 27-year-old multipara with five viable pregnancies, each complicated by the syndrome of chorea gravidarum. The characteristic symptoms occurred during the last trimester of each pregnancy and were not accompanied by fever or joint manifestations. The babies were all under 5 pounds, but all were living and well. The patient has apparently not shown any serious sequelae. Neurologic consultation ruled out any possibility of epilepsy or other convulsive disorders. Transient slight albuminuria and elevated plasma uric acid were the only signs suggestive of a possible associated toxemia. At this writing, the patient is in the first trimester of another pregnancy and is asymptomatic.

References

1. DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1947, W. B. Saunders Co.
2. Beck, A. C.: Obstetrical Practice, ed. 5, Baltimore, 1951, Williams & Wilkins Company.
3. Willson, P., and Preece, A. A.: Arch. Int. Med. 49: 471, 1932.
4. McElin, T., Lovelady, S., and Woltman, H.: Am. J. Obst. & Gynec. 55: 992, 1948.
5. Beresford, O., and Graham, A.: J. Obst. & Gynaec. Brit. Emp. 57: 616, 1950.

HYDATIDIFORM MOLE IN A 54-YEAR-OLD PATIENT

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HYDATIDIFORM mole has been described as far back as the fifth century by Aetius. In 1827 it was described as arising from the chorion.[1] Marchand in 1895 stated that the syncytium and Langhans cells undergo proliferation and that the stroma has little to do with the process.[2]

The incidence is usually given as 1:2,000 to 1:3,000 normal deliveries[3] but an incidence of 1:145 has been quoted as occurring in the Philippines.[4] It is therefore an uncommon but not a rare disease and may be the precursor of chorionepithelioma. Most authors quote an incidence of approximately 1 per cent of moles which change to chorionepithelioma.[3] We present this case not because of the rarity of the disease but because of the rarity of the disease at this age. Novak[5] and Hertig[6] state that they in their experiences have never had a case at this late age.

Case Report

Case No. 52-13099. This was the second admission of a 54-year-old white woman who entered the hospital on Oct. 18, 1952, with a chief complaint of a brownish vaginal discharge for ten days and marked vaginal bleeding for three days.

Her past history revealed that she had had acute diverticulitis five years before, treated conservatively. Removal of a cataract from the right eye had been performed four years before. She had had two children, 30 years and 22 years ago. No abortions, no abnormalities of pregnancy or puerperium were reported.

The menstrual periods had been regular except for one occasion one year ago when the patient had an episode of profuse vaginal bleeding with passage of clots which lasted about five days. The last menstrual period was Oct. 8, 1952, and the previous menstrual period, Sept. 10, 1952.

The systemic review was essentially negative. Physical examination revealed a middle-aged, well-nourished, slightly obese white woman in apparent good health. Examination was essentially negative except for the vaginal examination. This revealed a multiparous introitus, and a vagina filled with large blood clots. The cervix was large, succulent, and admitted one finger. The uterus was slightly enlarged. No masses could be palpated in the adnexa.

Laboratory Data on Admission.—Complete blood count showed 3,560,000 red blood cells; the color index was 0.97 Gm.; the hemoglobin was 68 per cent; the white blood count was 11,300, with 77 per cent polymorphonuclear leukocytes, 5 per cent eosinophils, and 18 per cent lymphocytes. Urinalysis was negative. The Aschheim-Zondek test was positive (reported after curettage).

Course.—On the basis of history and vaginal examination a diagnosis of incomplete abortion was made. A dilatation and curettage were done on October 18 and a large amount of tissue resembling white rice was recovered; bleeding was minimal. Pathological examination revealed a hydatidiform mole with proliferative trophoblastic syncytial elements with no suggestion of anaplastic activity in the Langhans cells.[7] A qualitative Aschheim-Zondek test was positive at the time of the curettage.

The patient was given 500 c.c. of blood for the slight anemia and on the basis of the pathological diagnosis and age of the patient a total hysterectomy with bilateral salpingo-oophorectomy was done on October 21. At the time of operation the uterus was soft and enlarged, with a fibroid on its fundal portion. The tubes and ovaries were normal. Pathological examination of the uterus revealed no remnants of hydatidiform mole.

A chest plate was done on October 24 to complete the investigation of this case. This was negative. On October 29 after an uneventful postoperative course the patient was discharged. An Aschheim-Zondek test performed six weeks postoperatively was negative.

Summary

A case of hydatidiform mole in a 54-year-old woman is presented (her age having been verified by a birth certificate). Because of her age and the precancerous status of this lesion, a total hysterectomy and bilateral salpingo-oophorectomy were done. Postoperative Aschheim-Zondek tests have been negative.

References

1. Dorr, E. M.: Nebraska M. J. **35**: 8, 1950.
2. Marchand, F.: Monatschr. f. Geburtsh. u. Gynäk. **1**: 419, 1895; Ztschr. f. Geburtsh. u. Gynäk. **32**: 405, 1895.
3. Gordon C., Rosenthal, A. H., and O'Leary, J. L.: Am. J. Surg. **85**: 194, 1953.
4. Greenhill, J. P.: The 1952 Year Book of Obstetrics and Gynecology, Chicago, 1952, The Year Book Publishers, Inc., p. 65.
5. Novak, E.: Personal communication.
6. Hertig, A.: Personal communication.
7. Novak, E.: Personal communication.

147-15 46TH AVENUE, FLUSHING, N. Y.

OSTEOGENESIS IMPERFECTA

A Case Report

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THIS case of osteogenesis imperfecta is reported because of its rarity and its apparent occurrence in three successive generations. Since the fetus in this disorder is usually stillborn, or dies in the early neonatal period, the report of the delivery of a fetus affected with the disease, by a mother who is also a victim of the disease, should be of interest.

The rarity is such that Gain and Lawson[1] report an incidence of one in 7,951 deliveries while other authors cite even higher statistical ratios. Eastman believes it is closer to one in 30,000. Osteogenesis imperfecta appears to have a definite familial and hereditary tendency. Kellogg[2] found this disease in five generations involving seventeen members of a family, nine of whom had suffered multiple fractures. Reisenman and Yater[3] studied the disease in five and seven successive generations. Its etiology is unknown but abnormal genesis of bone appears to be a developmental defect of the mesenchyme.

The disease is characterized by fragility of bone, as manifested by the occurrence of numerous fractures when minimal force is applied to the bones. Blue scleras, otosclerosis, and relaxed ligaments may also be associated with the condition. Brickley[4] found fragility of bones in 60 to 70 per cent of patients with blue scleras. The condition has been described in the literature as Vrolik's syndrome, fragilitas ossium, Lobstein's disease, and osteopsathyrosis. It differs from true achondroplasia or chondrodystrophy calcificans in which fractures are rarely seen.

Osteogenesis imperfecta is generally classified as congenita or tarda depending on whether the fractures are first seen at birth, at infancy or even later in life (osteopsathyrosis). With the congenita form the fetus is usually dead or dies soon after birth, but occasionally survives and remains a chronic invalid manifesting gross skeletal deformities, dwarfism, and generalized muscular atrophy. The pathology is mainly in the long bones of the extremities, though the calvarium or ribs may be involved in varying degrees. Radiologically, the cortex is seen to be thin and osteoporotic with a wide medullary cavity. Often there is evidence of callus formation in some portion of the bone shaft giving mute testimony to a recent fracture.

Normally bones are formed as a result of the activity of osteoblasts on connective tissue membrane, as in the formation of facial and cervical bones,

and on cartilage in the other bones with the process of absorption and bone formation occurring in proper ratio. Gordon[5] in 1928 stated that in osteogenesis imperfecta, bone formation remains in the primary fibrous state. "There is either a failure on the part of the osteoblast to form periosteal bone or the normal ratio of absorption and bone formation is lost. Osteoporosis is secondary and results from excessive formation of medullary spaces. Cartilage is not materially altered." This concept appears to hold true today.

Serum calcium and phosphorus are usually within normal limits. Treatment has been futile and is mainly symptomatic.

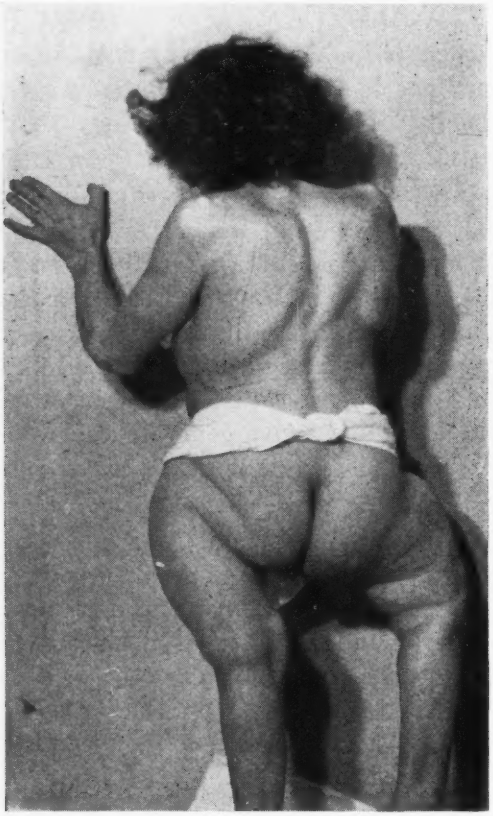

Fig. 1.—Posterior view of patient showing distorted bones and pelvis.

Case Report

M. W., a 32-year-old primigravida, reported to St. Catherine's Hospital clinic during her eighth month of pregnancy. She was a small squat woman, 4 feet tall, who appeared somewhat older than her actual age. The scleras were bluish in color. There was a marked widening of the anteroposterior diameter of the chest with kyphoscoliosis of the dorsal spine. Heart and lung findings were not unusual. The abdomen was enlarged to the size of an eight months' gestation. The lower limbs were markedly distorted and shortened. Roentgenograms of the pelvic abdomen showed a small gynecoid pelvis with marked asymmetry and curvature of the lumbodorsal spine. The fetus was small and unengaged with deformity and angulation of the left femur at the junction of the proximal and middle thirds. Nothing unusual was noted about the calvarium.

The patient stated she had sustained repeated fractures of both femurs, left tibia, and both arms, the first fracture occurring at 3 years of age, and the last when she was 25 years old.

She stated that her mother was of similar stature, with blue scleras, and had given birth to two babies, both spontaneously. The patient's sister did not have the disease.

After a normal antenatal course, she was admitted to the hospital for further study as to the best method of delivery. Medical consultation was obtained to evaluate the kyphoscoliosis. Blood count and urinalysis were normal. Calcium was 8.5 mg. per cent; acid phosphatase 3.2 and alkaline phosphatase 7.0 King Armstrong units.

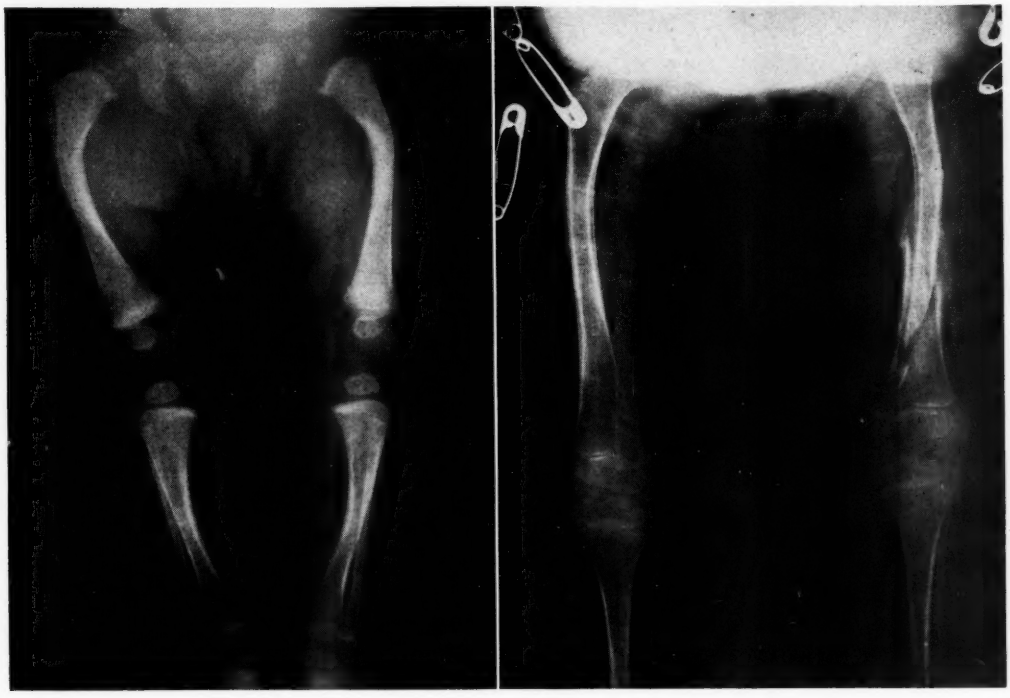

Fig. 2. Fig. 3.

Fig. 2.—X-ray of newborn showing osteogenesis imperfecta.
Fig. 3.—X-ray of infant at 13 months with fracture of left femur.

On Nov. 30, 1950, after twelve hours of labor, aided by small doses of Demerol, she was delivered spontaneously with episiotomy under local anesthesia, of a living female infant who weighed 5 pounds, 3½ ounces, in apparently good condition. Physical examination of the fetus revealed large anterior and posterior fontanelles and wide sutures. The bones of the calvarium were soft and wormian bones were palpable. The scleras were bluish gray. The thighs and legs were bowed. X-ray of the fetus shortly after delivery was reported as follows: "Outward curvature of upper shaft of femora indicating some degree of osteogenesis imperfecta. The possibility of old healed fractures intra-uterine must be considered through both shafts of the femurs. Moderate degree of lacunar formation in the skull."

Both mother and child were discharged in good condition. Thirteen months later, the child was readmitted to the hospital for fracture of the left femur. Eighteen months later the patient was again delivered spontaneously. This time the fetus showed no evidence of osteogenesis imperfecta.

References

1. Gain, D. D., and Lawson, D. E.: Radiology **58**: 221, 1952.
2. Kellogg, C. S.: Arch. Int. Med. **80**: 358, 1947.
3. Reisenman, F. R., and Yater, W. M.: Arch. Int. Med. **67**: 950, 1941.
4. Brickley, D. W., Jr.: Arch. Otolaryng. **46**: 230, 1947.
5. Gordon, C. A.: AM. J. OBST. & GYNEC. **16**: 214, 1928.

795 BUSHWICK AVENUE

A REPORT OF THREE CASES OF ADENOMYOSIS WITH ASSOCIATED TUBERCULOSIS*

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THE association of tuberculosis with adenomyosis is a rare but well-established condition. In Cullen's monograph no case was reported. In Prof. Stewart's chapter on "Endometriosis and Adenomyoma" in *Teacher's Manual of Obstetrical and Gynaecological Pathology* he has a short article on this subject in which he refers to three cases encountered in Leeds,[1, 2] and one reported by Dickson.[3]

The first case reported appears to be that of von Recklinghausen[4] in 1896, and he had a second case subsequently. Lockstädt[5] reported a case in 1898. Since that time, many single cases have been reported, a few workers have reported two cases, and de Almeida[6] has reported three cases in a single paper.

In 1939 Köberle[7] reported a case and reviewed the world literature, finding 21 cases. However, he had missed a few, mainly in the British journals. I have found thirty-five cases (Table I).

Table I

AUTHOR	NUMBER OF CASES	DATE
Von Recklinghausen	2	1896
Von Lockstädt	1	1898
Vaszman	1	1899
Lichtenstern	1	1901
Hösli	1	1904
Dickson	1	1906
Archambauld and Pearce	1	1907
Grünbaum	1	1907
Schütze	1	1907
Schottländer	1	1913
Lindquist	1	1913
Kundrat	2	1920
Bertolini	1	1921
Meyer	1	1924
Johnstone	1	1924
Kitai	2	1924 and 1926
Daniel	1	1925
Gaifami	1	1925
Heesch	1	1928
Terasvouri	1	1931
Vaux	1	1932
Stewart and Oldfield	2	1932 and 1935
Stewart C.	1	1933
Köberle	1	1939
de Almeida	3	1939
Fernandez-Riuz	2	1945
Volta	1	1948
de Soldenhoff	1	1948

*Read at the Annual Meeting of the Ontario Association of Pathologists, in Toronto, Oct. 31, 1952.

The present series is of three cases coming to our Laboratory within two and one-half years.

CASE 1.—M. L. was a 46-year-old woman. Her chief complaints were low back pain and dysmenorrhea with clots for ten to twelve months. Previous to that time, there had been no abnormality in her menstrual history.

The pertinent family history concerned two brothers, one of whom died of tuberculosis at the age of 36, and another who had been admitted to a sanatorium recently.

Fig. 1.

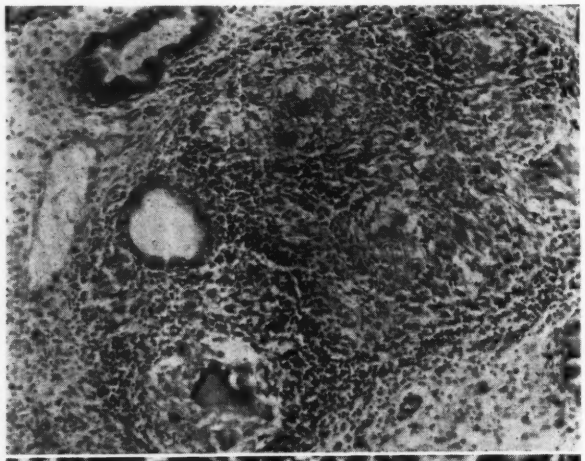

Fig. 2.

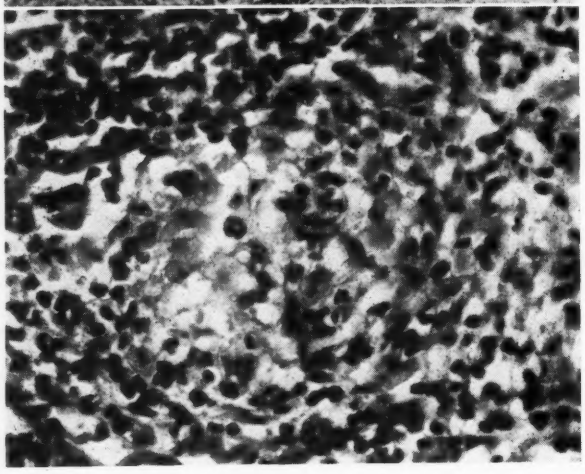

Fig. 1 (Case 1).—Low-power view of endometrium showing tubercle without caseation.
Fig. 2 (Case 1).—Higher magnification of tubercle in endometrium.

She was married at the age of 17 and had 6 children, all of whom died in infancy (1 hour, 2 days, 19 months, 2½ months, 28 days, 5½ months). Two adopted children are healthy.

In 1927 she had a right oophorectomy and a small tumor removed.

The clinical examination (including chest x-ray) was essentially negative except for the pelvis. Pelvic examination revealed a painful mass in the left pouch of Douglas and a uterus enlarged to the size of a 3 months' pregnancy. The cervix was large but not ulcerated. A subtotal hysterectomy and left salpingo-oophorectomy were performed.

At our laboratory we received approximately one-half of the body of an enlarged uterus, with an attached short stump of Fallopian tube and an ovary. There were a few fibrous adhesions on the serosal surface of the uterus. The cut surface had the typical whorled appearance found in adenomyosis. This was widespread and diffuse with no encapsulated masses. There were numerous small softened areas containing creamy material.

Microscopic examination of the endometrium revealed a chronic inflammatory process which was granulomatous in nature with numerous tubercles (Figs. 1 and 2). In the myometrium adenomyosis was widespread. In the stroma of these islands of endometrial tissue numerous tubercles were encountered (Fig. 3). Some of these were extremely large with huge areas of central caseation corresponding to the softened areas noted macroscopically. No tubercles were found in the fibromuscular tissue of the myometrium.

No tuberculosis or endometriosis was found in the ovary. In the Fallopian tube there was a multinucleated giant cell in the mucosa but no definite tubercle.

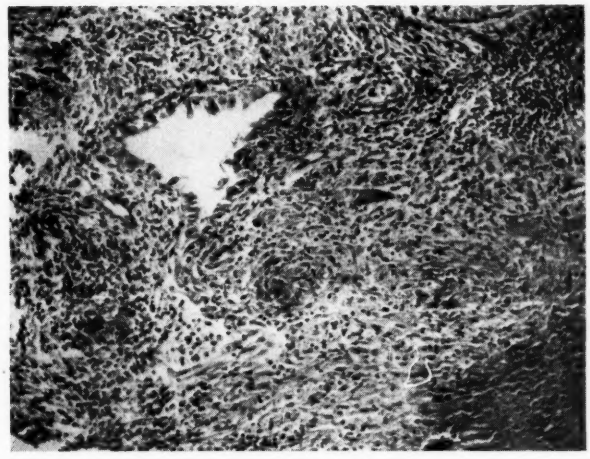

Fig. 3 (Case 1).—Low-power view in an area of adenomyosis. One gland is visible in which the lining epithelium is partially destroyed. This area is adjacent to massive caseation.

CASE 2.—N. H. was a 55-year-old woman. Menstruation ceased four years ago at the age of 51 and there was amenorrhea for thirteen months. For the last three years, however, she had been flowing excessively each month so that she had to remain in bed during the period.

Her previous history stated that she had 4 apparently normal pregnancies with 4 living children between the ages of 20 and 36 years.

Twenty-two years ago she had been operated upon for tuberculous peritonitis. One ovary and the appendix were removed at that time. She had marked ascites postoperatively, with tubal and sinus drainage for some time.

A subtotal hysterectomy was performed. The uterus was removed with some difficulty due to the obesity of the patient and the fact that the uterus was attached by firm adhesions to the bladder, bowel, and omentum.

We received the body of the uterus which was enlarged and measured 9 by 6 by 5 cm. The serosa was roughened and dark gray. Sections revealed one encapsulated area with a coarsely whorled appearance which measured 4 cm. in diameter. In addition, there was a large poorly defined coarsely whorled area occupying the upper part of the fundus. There were softened yellowish-gray areas which exuded thick material on pressure. The endometrium was thin with some adherent brownish-red material.

Microscopic examination revealed an endometrium in which there was a good deal of postoperative autolysis, with some loss of superficial tissue. In the well-preserved areas there were numerous tubercles. The encapsulated area was a fibromyoma with no evidence of either adenomyosis or tuberculosis.

The diffuse whorled area was composed of many islands of endometrial stroma surrounding endometrial gland acini. In these islands there were numerous tubercles, many with central caseation. These areas of caseation were not so large as in the previous case.

CASE 3.—M. J. was 53 years of age and her chief complaint was one of profuse menstruation for two years and shortly before admission to the hospital one episode of intermenstrual bleeding.

Her past history yielded very little. In 1918 she had a severe attack of influenza with pneumonia but no sequelae. Shortly after that she was vaccinated and the arm became swollen. It subsided shortly but she was bedridden for a year with what she described as sciatica and neuritis. After that time she was in good health. One interesting point is that she is a nullipara and twenty years ago had a suspension operation in the hope of becoming pregnant. Her menstrual history until two years ago was relatively normal except for slight irregularity.

There was no history of close contact with tuberculosis. She remembered occasionally visiting a family about twenty years ago of whom members subsequently died of tuberculosis.

The specimen we received consisted of the whole uterus, both ovaries, and the Fallopian tubes. The uterus was large but unfortunately it had been cut transversely as well as longitudinally so that accurate measurement was impossible.

The myometrium in the fundus had a diffuse, coarsely whorled appearance. There were areas of softening, yellow in color, and measuring up to 0.4 cm. in diameter. On pressure thick creamy material exuded. In addition to this, there were several small fibromyomas which measured up to 1.5 cm. in diameter. The endometrium was 0.3 cm. in thickness.

The larger ovary measured 6 cm. and the smaller one 4 cm. Section revealed a large cyst in each replacing most of the tissue. The cysts were partially filled with pale yellow soft material which resembled hemolyzed blood clot. The Fallopian tubes were incomplete, lacking the fimbrial ends. They were both thicker than usual and section revealed thick walls and a swollen mucosa so that the lumina were obliterated in some areas.

The microscopic appearance was similar to that of the two previous cases, with small tubercles in the endometrium in which central caseation was encountered only occasionally. In the areas of adenomyosis there were very large lesions with huge areas of caseation. In this case the inflammatory process was so marked that there was wide destruction of the adenomatous tissue, although in most of the lesions traces of acini were found. In a few areas, however, I could not be absolutely certain that they were confined to the area of adenomyosis and not lesions extending into the myometrium. The general appearance so closely resembled the others except for the absence of acini that I believe these, too, were actually areas of adenomyosis.

No tuberculosis was found in the fibromyomas.

In the ovaries there was endometriosis but no tuberculosis. In the mucosa of both Fallopian tubes there were numerous well-formed tubercles.

One striking feature in the reported cases was the number of nulliparous patients. In many of the cases, as in two of ours, there was no other tuberculous lesion demonstrated.

Several theories have been advanced: (1) that the association is accidental with tuberculous infection occurring secondarily in an already existing adenomyosis; (2) that it is a secondary infection because of a previous predisposition; (3) that the adenomyosis is a consequence of the tuberculous infection. Köberle puts it thus, "On account of the local association of both processes and their histological character in this case it is thought that there is a causal relationship between adenomyosis and tuberculosis, in that sense that the tuberculosis was the causative agent for the internal adenomyosis of the uterus where a previous preparedness of the myometrium for adenomyosis existed."

Summary and Conclusions

1. Three cases of adenomyosis with associated tuberculosis have been reported.

2. Except for minor differences these cases are essentially similar.

3. The absence of tuberculous infection in the ovarian endometriosis in Case 3 seems to substantiate the theory that this is an accidental association.

References

1. Stewart, M. J., and Oldfield, C.: J. Obst. & Gynaec. Brit. Emp. **39**: 759, 1932.
2. Stewart, Clara: J. Obst. & Gynaec. Brit. Emp. **40**: 299, 1933.
3. Dickson, T. G.: Am. J. Obst. **53**: 799, 1906.
4. Von Recklinghausen, F. D.: Die Adenomyome und Cystadenome des Uterus und Tubenwandung, ihre Abkunft von Resten des Wolffschen Körpus, Berlin, 1896, Kap. 8.
5. Von Lockstädt, P.: Monatschr. f. Geburtsh. u. Gynäk. **7**: 188, 1898.
6. de Almeida, F., and Horta, J. da Silva: Arq. de obst. e. ginec. **4**: 251, 1939.
7. Köberle, F.: Wien. Klin. Wnchschr. **52**: 122, 1939.

TUBERCULOSIS OF THE CERVIX

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THE treatment of tuberculosis of the pelvis offers several avenues of approach including antibiotic drugs, surgery, and such proved basic principles as rest, vitamins, and good nutrition. In the younger woman radical surgical treatment is being replaced by more conservative efforts in order to preserve the childbearing function. The experience of those treating pulmonary tuberculosis is so wide that it may serve as a valuable guide in treating pelvic tuberculosis. The authorities in the field of pulmonary tuberculosis have led the way in outlining and perfecting chemotherapy.

Case Report

Mrs. G. T., a Negro woman aged 25 years, was seen in August, 1951, with the complaint of bleeding after intercourse and moderately profuse blood-tinged vaginal discharge. Bleeding was in small amounts but at frequent intervals so that it was not characteristic of any regular menstrual period. Menstruation began at the age of 13 years. At that same age the patient underwent surgery for tuberculosis of the hip. Menstruation discontinued after the hip surgery and no further vaginal bleeding appeared until after the time of her marriage which was 2½ years previous to this examination. Complaints other than vaginal spotting were periodic suprapubic and left lower quadrant pain. There was dyspareunia at times.

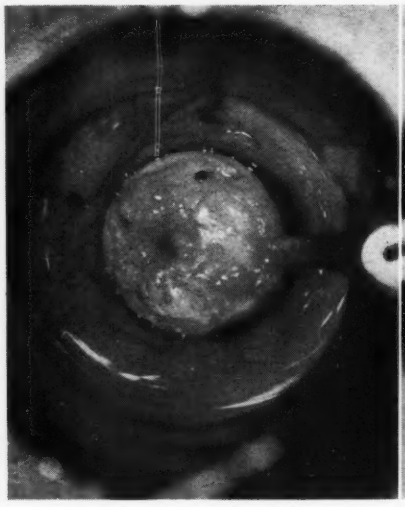

Fig. 1.

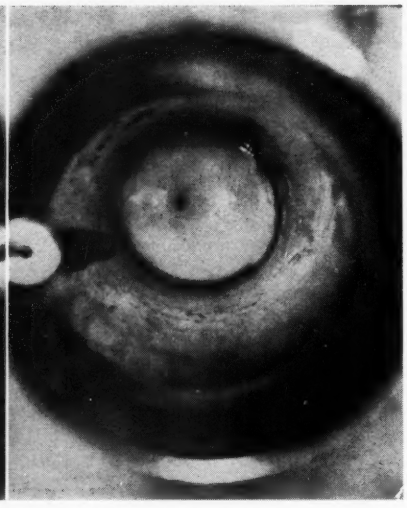

Fig. 2.

Fig. 1.—Tuberculosis of cervix before treatment.
Fig. 2.—Healed cervix after 70 days' treatment.

Pelvic examination revealed a large cervix with the entire surface eroded and with numerous polypoid projections on the lower lip. The eroded surface of the cervix was so friable that contact by a cotton applicator resulted in bleeding. The uterus was slightly

enlarged. The left adnexa were easily palpable, being about twice normal size. Biopsy of the cervix and uterine curettage were done with a preoperative diagnosis of cervical malignancy. The pathological diagnoses of the tissues removed were: 1. Fibrocaseous tuberculosis of the cervix. 2. Tuberculous endometritis and endocervicitis.

The medical treatment consisted of dihydrostreptomycin, 2 Gm. daily 6 days a week, as recommended by Sered, Falls, and Zummo.[2] Surgically the cervix was treated by light cauterization at monthly intervals by electrocautery. The purpose of light cauterization was to inhibit some of the secondary invaders and thus provide a cleaner surface for new squamous epithelium to bridge across. The activity of the tubercle bacillus would not be altered by the local treatment.

The accessibility of the cervix for direct inspection by speculum examination made it a unique organ in which to note the progress of recovery in such a disease as tuberculosis. Evidences of gradual healing made themselves manifest on the eroded areas of the cervix soon after treatment began. At the end of 3 weeks' treatment the left adnexa had returned to normal size. The cervix was healed after 70 days' treatment with pink healthy squamous epithelium replacing the entire eroded area. The first menstrual period appeared 46 days after the beginning of treatment and regular monthly menstrual periods of 2 days' duration have continued. Treatment was discontinued more than one and one-half years ago, during which time the uterus and adnexa have remained normal in size and there have been no pelvic symptoms. It is not likely, but yet one entertains the hope that this patient may sometime become pregnant.

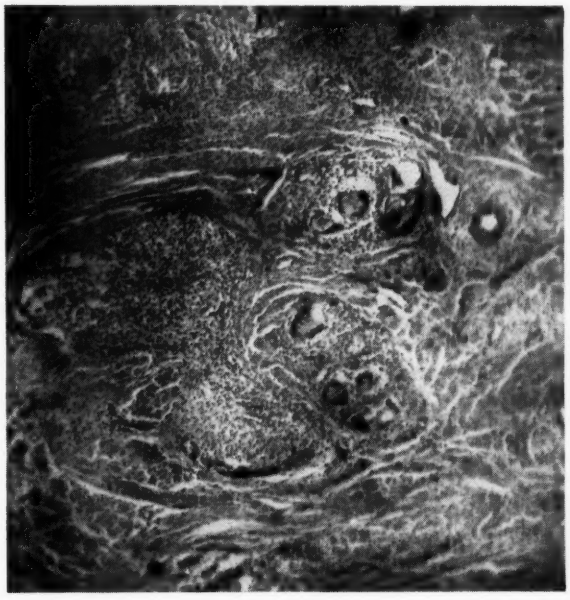

Fig. 3.—Microscopic section of cervix showing tubercles and giant cells.

This patient was known to have tuberculosis of the hip at the age of 13, but the first indication of vaginal bleeding occurred after marriage at the age of 23. At what age this patient developed tuberculosis of the pelvis is not known but it may have been as early as the age of 13. The dihydrostreptomycin treatment undoubtedly cleared up the tuberculosis of the uterus and adnexa, permitting a relatively normal menstrual cycle and menstrual flow to return and to continue. The lungs of this patient are negative for tuberculosis and periodic chest x-rays through the past twelve years have always been negative.

The period of this treatment extended over 70 days with 60 intramuscular injections of 2 Gm. dihydrostreptomycin and 3 cervical cauterizations. Streptomycin in this dosage and with daily frequency may often cause reaction. This patient had one week of disturbing dizziness after about 40 days' treatment, but it was not necessary to discontinue the injections.

Excellent summaries of present-day drug therapy in pulmonary tuberculosis are given by Temple[3] and by Carr.[1] From these suggested combinations the gynecologist may well select drugs suitable for his patient.

More recent experience has demonstrated that streptomycin may be given less frequently than was used in this case, and in such combinations as the following: (1) streptomycin, 2 Gm. intramuscularly every three days, combined with para-aminosalicylic acid, 12 Gm. daily given orally; or (2) streptomycin, 2 Gm. intramuscularly every three days, combined with Terramycin, 5 Gm. daily given orally.

References

1. Carr, D. T.: J. A. M. A. 150: 1170, 1952.
2. Sered, H., Falls, F. H., and Zummo, B. P.: J. A. M. A. 142: 547, 1950.
3. Temple, C. W.: J. A. M. A. 150: 1165, 1952.

ENDOMETRIOSIS OF THE BOWEL SIMULATING CARCINOMA*

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ENDOMETRIAL lesions of the lower bowel may be quite difficult to diagnose grossly, since they may, so often, closely simulate carcinoma. In similar fashion, bowel lesions in women who have pelvic endometriosis may, nevertheless, prove to be carcinoma. The coexistence of these pathologic processes has recently been reported by Hawthorne, Kimbrough, and Davis.[1] Indeed, a great deal of care must be exercised in the diagnosing and treating of such cases.

A case which rather clearly demonstrates these diagnostic pitfalls is presented here.

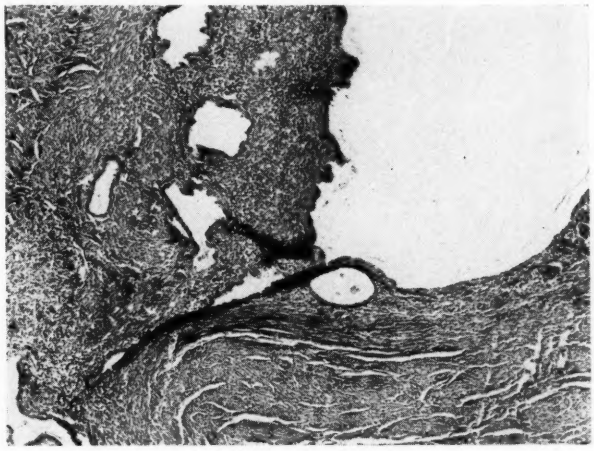

Fig. 1.—Typical endometriosis of the left tube. (×50. Reduced one-fifth.)

Case Report

The patient, R. F., a 53-year-old housewife, was admitted to the Gynecologic Service, Sept. 15, 1952, with the chief complaints of menorrhagia, weakness, and easy fatigability. Her periods of late had been irregular, were lengthened in duration, and there was considerable increase in the menstrual flow. There were no bowel or urinary complaints and the past medical and surgical histories were negative.

Physical examination revealed a white woman in no obvious distress. The heart, blood pressure, and lungs were normal. The abdomen was soft and nontender, although a mass arising from the pelvis could be palpated. Bimanual vaginal examination revealed a uterus grossly and grotesquely enlarged to the size of a three months' gestation. The impression of a soft, cystic mass to the left of the uterus was obtained. The cervix was clean and healthy, and the rectal examination revealed no abnormalities. A clinical diagnosis of multiple myomas of the uterus and left ovarian cyst was made.

Hemogram, blood chemistry, and urine were normal. An intravenous urogram revealed normally functioning kidneys but evidence of depression of the bladder dome by

*Read at a meeting of the Obstetrical Society of Philadelphia, April 2, 1953.

an extrinsic mass. Vaginal and cervical Papanicolaou smears were reported as Class II (atypical cells present but no evidence of malignancy). No preoperative bowel studies were done.

A laparotomy was performed Sept. 17, 1952. The expected uterine myomas were found. There were in addition, however, numerous bluish areas with the gross appearance of endometriosis throughout the pelvis. The left ovary contained a lemon-sized "chocolate cyst," and there were numerous pelvic adhesions. A subtotal hysterectomy with bilateral salpingo-oophorectomy was performed. As the large intestines were being replaced in the pelvis, prior to the usual prophylactic appendectomy, a constricting lesion of the large bowel, approximately eight inches from the distal end, was found. The serosa covering the lesion appeared unaffected and the lesion itself was felt to be within the bowel wall. Because of the uninvolved serosa and the nature of the lesion itself, a clinical diagnosis of carcinoma of the colon was made and since there had been no preoperative preparation of the bowel, it was decided to delay further surgery.

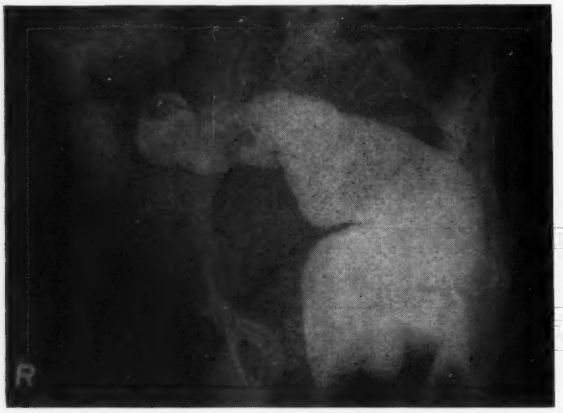

Fig. 2.—Barium enema x-ray of sigmoid, demonstrating almost complete obstruction.

The pathologist's report on the extirpated material was: *Uterus:* fibromyomas, submucous fibromyoma, focal cystic endometrial hyperplasia. *Ovaries:* hemorrhagic follicle cysts, left. *Oviduct:* endometriosis, left (Fig. 1).

The patient's postoperative condition was good until the fourth day when she developed symptoms of bowel obstruction. Signs progressed rapidly. A Miller-Abbott tube was passed and provided a small measure of relief after it traveled beyond the pylorus. A barium enema at this time revealed a constricting lesion of the lower sigmoid, reported as "most likely carcinoma" (Fig. 2).

The patient was reoperated upon on the tenth postoperative day. An adhesion of the small bowel with kinking was found to be producing almost complete obstruction. This adhesion was released and the injured serosa of the bowel repaired. The sigmoid colon lesion was unchanged. A left hemicolectomy with end-to-end anastomosis was then performed. Following this surgery, the patient then made a complete, smooth, and uneventful recovery.

Gross pathologic examination of the constricting lesion of the sigmoid seemed to substantiate the clinical impression of carcinoma. The specimen consisted of a segment of large bowel measuring 28 cm. in length. Seven cm. from one resected end there was an acute angulation. At this angle there was a lesion 1.5 cm. in extent which appeared to involve the majority of the circumference of the wall and to replace the wall by a tannish, white tissue which had a streaked appearance. The serosa remained intact but the pattern of the mucosa overlying the indurated area was lost. No lymph nodes were identified.

Microscopically, however, the picture was different and the pathologist reported: Sections revealed an area of irregular hyperplasia of the muscular elements of the bowel

wall within which were seen numbers of glandular stromal elements typically endometrial in origin (Fig. 3). The lesion does not appear to extend into the serosa (Fig. 4). No malignancy is seen.

Pathologic diagnosis: Colon, endometriosis.

Fig. 3.

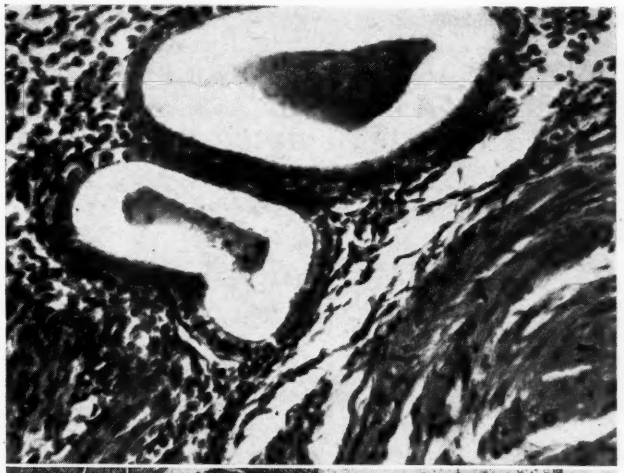

Fig. 4.

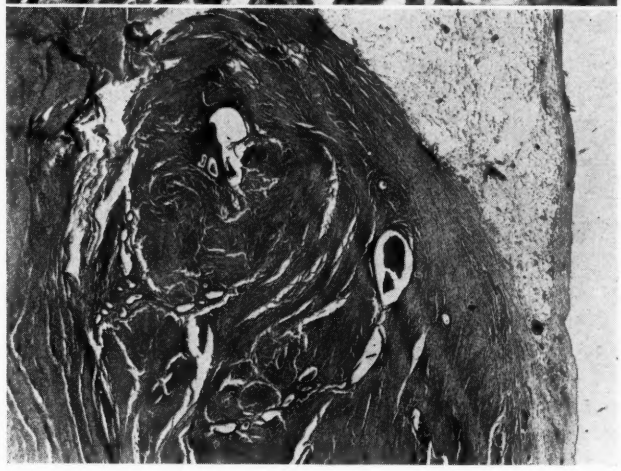

Fig. 3.—Endometriosis of colon. (×250. Reduced one-fifth.)

Fig. 4.—Intact serosa overlying endometriosis of the sigmoid colon. (×15. Reduced one-fifth.)

The gross differential diagnosis between endometrial lesions and carcinoma may be difficult. Clinically the problem is made even more difficult by the possibility that the two entities may be present at the same time.

The case here presented represents a lesion of the large bowel that clinically had all the appearances of carcinoma but which proved, on histologic examination, to be endometriosis. It is most interesting to note that the serosa covering the bowel lesion was not involved. This could lead to much speculation as to the origin of the endometriosis in this area.

Reference

1. Hawthorne, H. R., Kimbrough, R. A., Jr., and Davis, H. C.: Am. J. Obst. & Gynec. 62: 681, 1951.

255 South 17th Street (Dr. Weber)

THE SURGICAL RELIEF OF DYSMENORRHEA PRODUCED BY HEMATOMETRA IN A RUDIMENTARY HORN OF A UTERUS BICORNIS UNICOLLIS

Report of One Case

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THE frequency of occurrence of congenital anomalies of the female genital tract is difficult to evaluate and has been reported to vary from 0.004 to 3.8 per cent.[1, 2, 3]

A recent survey at this hospital revealed an incidence of 0.3 per cent in 3,127 deliveries.[4]

One of the more serious complications due to anomalies of the uterus is pregnancy in a rudimentary horn of a uterus bicornis unicollis. This anomaly is classified by Jarcho as uterus bicornis uno latere rudimentarius.[5]

This case is presented to show a gynecologic complication attributable to a uterus bicornis unicollis with a rudimentary horn.

Case Report

B. B., a 20-year-old gravida ii, para ii, was first seen in the outpatient clinic with the chief complaint of dysmenorrhea. The pain had been present since the menarche at age 13 years and was described as persistent, dull with occasional sharp cramping, limited to the right side, and radiating down the medial aspect of the right thigh. The pain began on the first day of the period and gradually subsided six to eight days after the usual five days' flow.

At age 16 years, an exploratory laparotomy was performed because of the dysmenorrhea and the right ovary and appendix were removed without clinical improvement.

The patient had two full-term pregnancies and delivered live infants without complication. No pain was present during either pregnancy.

The general physical examination at the time we first saw the patient was noted to be normal. On pelvic examination some thickening of the right adnexal region was encountered. The uterus was retroverted, but easily reposited and maintained in position by a pessary. Oral androgen therapy provided some lessening of the pain.

Other studies including intravenous pyelograms, barium enema, x-rays of pelvis and lumbosacral area, complete blood count, urine analysis, and sedimentation rate were all normal.

Repeated pelvic examinations were noninformative until an examination was performed during menstruation. A definite mass comparable in size with the fundus of the uterus was found to be present to the right of the uterus and attached to the uterus.

A hysterogram was performed revealing the outline of a uterus unicornis unicollis (Fig. 1).

A laparotomy was performed on Aug. 4, 1952, under spinal anesthesia.

The right ovary was surgically absent, as was all except the fimbriated end of the right tube.

There were two uterine cornua of equal size (Fig. 2). Palpation indicated that the right cornu failed to connect with the cervix. Aspiration of the cavity revealed the presence of a thick black fluid. The broad ligament was surgically detached from the rudimentary horn and the horn was removed. A good plane of cleavage was present in the sulcus between the cornua and the integrity of the wall of the left cornu was preserved. The broad ligament was then sutured to the left cornu. The round ligament was attached with interrupted chromic No. 0 sutures to the remaining horn.

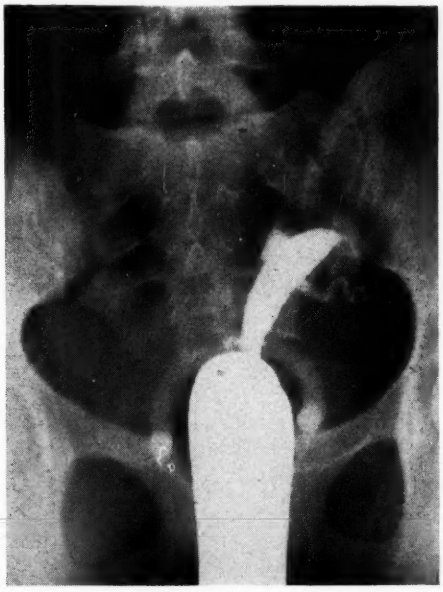

Fig. 1.—Hysterosalpingogram revealing picture of uterus unicornis unicollis in case of rudimentary right horn in uterus bicornis unicollis.

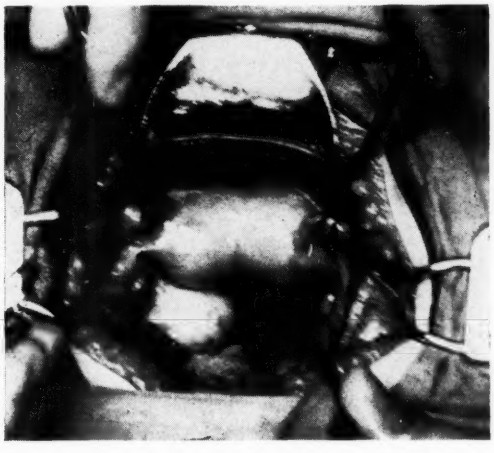

Fig. 2.—In situ pathology in case of rudimentary right horn in uterus bicornis unicollis. The right ovary and most of the right tube were removed at a previous laparotomy.

The postoperative course was complicated by fever due to hematoma formation in the right broad ligament.

The six weeks postoperative pelvic examination revealed the uterus in anterior position and freely movable. No induration was present in the right broad ligament. Since surgery the patient has been free of menstrual pain.

Conclusion

A case of uterus bicornis unicollis with a rudimentary right horn is presented. The anomaly was not diagnosed until a hysterogram was performed. Pelvic pain produced by the pressure created in the rudimentary horn was relieved by surgical extirpation of the horn.

References

1. Falls, F. H.: Am. J. Obst. & Gynec. 15: 399, 1928.
2. Kerr, J. M. M., and Moir, J. C.: Operative Obstetrics, ed. 5, Baltimore, 1950, Williams & Wilkins Company.
3. Smith, F. R.: Am. J. Obst. & Gynec. 22: 714, 1931.
4. Baker, W. S., et al.: In preparation.
5. Jarcho, J.: Am. J. Surg. 71: 106, 1946.

AN AID IN DRAPING PATIENTS FOR VAGINAL SURGERY

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IN ANY vaginal work, it is necessary to wall off the anus from the relatively sterile field of operation. The anus is usually walled off with a sterile towel, but the method of holding the towel in place varies in different hospitals. Some of the methods of holding the towel may be noted.

The towel may be held with adhesive tape running from one buttock across the perineum to the other buttock and stuck to the stirrups and skin. The objections to this are several. An occasional patient may get an allergic reaction to the adhesive tape. The tape may work itself loose as the patient perspires during the operation. Finally, the adhesive tape requires constant cleaning of the stirrups and its use is wasteful.

Another method is to use rubber tubing tied to the stirrups. The objection to this method is that the tubing often slips, and the towel is therefore often not in the center after one end of the tubing is fixed and the other is stretched and tied in place.

At the Columbia Hospital, Washington, D. C., we have devised a simple piece of apparatus which is known as "the two-way stretch."

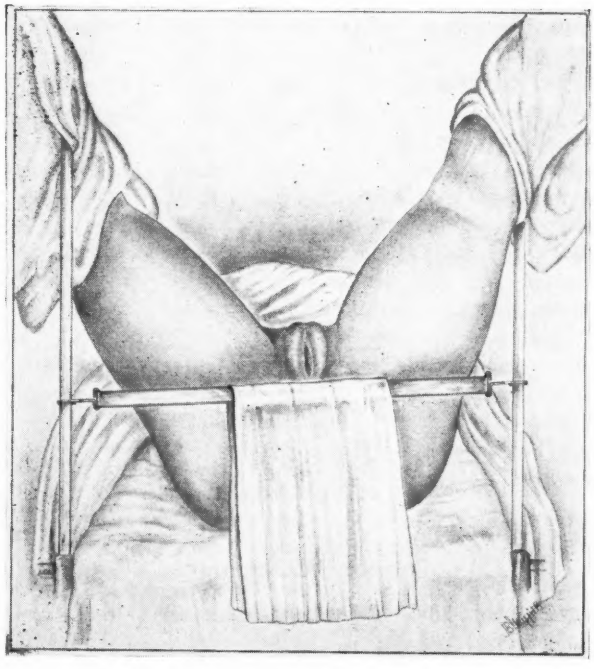

Fig. 1.

As shown in Fig. 1, it consists of a piece of rubber 7/8 inch in width with a hook on each end. The two hooks are held by the circulating nurse while the scrub nurse places a sterile towel over the center of the rubber straps. The circulating nurse then hooks the hooks onto the stirrups at the proper level so as to wall off the anus. The rubber strap has enough give so as not to interfere with the weighted vaginal speculum, if used.

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Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Anesthesia, Analgesia

Klink, Edward Walter: Perineal Nerve Block—An Anatomic and Clinical Study in the Female, Obst. & Gynec. 1: 137, 1953.

The sensory innervation of the vagina and perineum was studied by dissection of the sacral nerves on 85 cadavers, and by observation of the area of anesthesia produced when specific nerve roots were injected with an anesthetic agent. To confirm the anatomical and clinical studies more than 300 perineal nerve blocks were performed in obstetrical and gynecological patients.

It was found that the pudendal nerve innervates the lower vagina and the whole of the perineum, including the clitoris, the labia, and the entire perineal body. It was noted that the inferior hemorrhoidal nerve was a branch of the pudendal nerve in 50 per cent of the dissections, and in the other 50 per cent it began as a separate branch of the fourth sacral nerve. As a result of this study a technique for producing perineal anesthesia is presented. This consists of injecting 10 c.c. in equally divided amounts in three different areas in the pudendal canal, so that the pudendal nerve, the inferior hemorrhoidal, and the posterior femoral cutaneous nerve are blocked. One per cent Xylocaine without the addition of vasoconstrictor agents or hyaluronidase was used as the anesthetic agent. The clinical use of this method of anesthesia is discussed in carefully selected cases. It is satisfactory for spontaneous, also forceps delivery, for the performance and repair of episiotomies, and for breech deliveries. It is of particular value where it is necessary to avoid increased anoxia to the fetus. Pudendal block may also be used for removal of the Bartholin glands, biopsy of the vulva, and simple vulvectomy. The question of drug sensitivity is briefly presented.

ARTHUR V. GREELEY

Cancer, Malignancies

Freire, M. A.: Endometrial Cancer Before the Menopause, Rev. Soc. de Obst. y ginec. de Gordova R. A., Special number 19, 1951.

After reviewing the statistics of the important world clinics and those of the Clinica Ginecologica de Cordova, the author states that the concept of endometrial cancer as a condition found only in the postmenopausal period is erroneous. He reports on 102 cases of cancer of the endometrium treated at his clinic, of which 39 were premenopausal and 63 were postmenopausal. This corresponds with the reports of Mason and Gregg of the Mayo Clinic, and Speert of the Roosevelt Hospital in New York City, these clinics showing a 2 to 5 ratio. In the author's series, most of the postmenopausal cases occurred in patients whose menopause started between the ages of 45 and 55 years of age. The writer enumerates a list of clinical characteristics of this condition worthy of note. There exists

a relative frequency of this condition with functional tumors of the ovary, thecomas. It is also worthy of note that women who have been castrated do not seem to develop cancer of the endometrium. The author mentions hysterosalpingography and endometrial biopsy as the most important diagnostic procedures in determining the presence of endometrial cancer. He also makes a plea for gynecologists to think of cancer of the endometrium as a condition common in the premenopausal period, more common than it has been thought of until now.

RICARDO L. GORBEA

Lombard, H. L., Middleton, Margaret, Warren, S., and Gates, O.: Use of the Vaginal Smear as a Screening Test, New England J. Med. 246: 523, 1952.

An experimental study was made of the use of single vaginal smears in the diagnosis of uterine cancer, in order to determine whether the cytology test for cancer should be made available to the cancer clinics of Massachusetts either as a screening test for all female patients or as an additional diagnostic procedure for those with gynecologic conditions.

A single vaginal smear was obtained from each woman who attended the cancer clinics between Jan. 1, 1945, and June 30, 1947. Three years after the original smear, a follow-up history and, whenever possible, a pelvic examination and a repeat smear were secured to determine if cancer had developed in the interim. Those patients with positive or questionable original smears who showed carcinoma on biopsy or curettage were not followed further in this study.

The cost for collection and examination was slightly over $3.00 per specimen. The group of 1,654 women with no gynecologic symptoms produced 9 cancers, 3 of which were discovered by the smear. Thus, the cost per discovered case was approximately $1,700. The incidence of cancer among women without gynecologic symptoms was less than 1 per cent and among those with other gynecologic symptoms it was about 10 per cent. If questionable smears were omitted, erroneous diagnoses would be less than 1 per cent among symptomless women and nearly 8 per cent among those reporting bleeding. The percentage of questionable diagnoses was about four times as great among those with bleeding as among those who did not mention bleeding. The authors feel that the large error found among the group most likely to have cancer, the bleeders, impairs the value of this test as a diagnostic method for screening purposes. It does not seem feasible for a state health department to offer this test on an extensive scale for women without gynecologic symptoms, as the cost would be prohibitive and the number of cancers found would be relatively few.

The authors emphasize that in this discussion they are not concerned with the value of the vaginal smear as a means of diagnosis per se but rather with its use as a method of screening large populations. The value of this technique as a screening procedure is obviously limited as compared to its usefulness in the study of a given case.

IRVING L. FRANK

Brewer, John I., and Foley, Thomas J.: Endometrial Carcinoma and Hepatic Cirrhosis, Obst. & Gynec. 1: 67, 1953.

This report was provoked by Speert's conclusion that hepatic cirrhosis is five and one-half times more common in women with endometrial cancer than in those who do not have it. The entire autopsy experience of four general hospitals revealed 34 patients with endometrial cancer. None of these had cirrhosis. There were 144 women with hepatic cirrhosis but not one of these had endometrial cancer. There were 24 co-existing cancers, chiefly breast, bowel, and cervix. There is no increased frequency of endometrial carcinoma in patients with hepatic cirrhosis.

WILLIAM F. FINN

Rubio, Boris L.: Lesions of the Uterine Cervix, A Study of 500 Cases, Ginec. y obst. México **7:** 515, 1952.

The author reports on 500 cases of lesions of uterine cervix, studying these cases via colposcopy, vaginal cytology, the Schiller test, and cervical and endocervical biopsy. The author uses the Schiller test as a method of determining the site for tissue biopsy. By following this procedure he was able to arrive at the following results: cancer in situ, 3 cases; basal-cell carcinoma (Stage I), 1 case; spindle-cell carcinoma (Stage I), 3 cases; spindle-cell carcinoma (Stage II), 3 cases; spindle-cell carcinoma (Stage III), 3 cases; spindle-cell carcinoma (Stage IV), 4 cases; intermediary carcinoma (Stage III), 1 case; intermediate carcinoma (Stages III-IV), 1 case; adenocarcinoma (Stage III), 1 case; and benign cervical lesions, 480 cases.

The author's diagnostic criteria were based on the studies of Te Linde and Ulfelder in determining cases of cancer in situ.

All cases of cancer in situ and Stage I and Stage II were treated surgically by total hysterectomy, abdominal or vaginal, or by the Wertheim procedure with bilateral gland excision. Stage III and IV cervical cancers were referred for radiotherapy.

The percentages of the different lesions conform with those of recognized clinics outside of Mexico. The author considers tissue biopsy as the most valuable procedure in diagnosis, without belittling the importance of the other tests, such as the Schiller test, vaginal cytology, and colposcopy.

RICARDO L. GORBEA

Cesarean Section

Araujo, J. O., and Neme, B.: Cesarean Section Before and After Antibiotics, An. brasil. de ginec. **17:** 129, 1952.

The authors review 830 transperitoneal low cesarean sections at the Obstetrical Clinic of São Paulo's University to demonstrate the value of the prophylactic and curative use of the sulfonamides and antibiotic drugs in puerperal infections. With this in mind the section cases were divided into three groups: (1) 454 operations performed between 1931 and 1941 in which none of the above-mentioned drugs were used; (2) 161 performed between 1941 and 1945 in which sulfonamides were used, in 35 of which cases blood concentration studies of the drugs were made; and (3) 215 of which 40 cases were treated with sulfonamides only and the remaining 175 which were treated with combinations of sulfonamides, penicillin, and streptomycin.

To compare the results in all groups, the authors divided their cases according to the degree of infection actually present or suspected, considering symptoms of hyperthermia, suppurative wounds, peritonitis, and death to indicate the degree of the infection. In analyzing the various tables so classified, the authors conclude that because of the excellency of the antibiotics in preventing puerperal infections, they should be used as a prophylactic measure in all cases, including those that are clinically noninfected.

The authors outline the prophylactic treatment of puerperal infections in cesarean section cases as follows: 1,000,000 units of penicillin and 2 Gm. of dihydrostreptomycin in the abdominal cavity during operation. This is followed by the daily administration of 400,000 units of procaine penicillin and 0.5 Gm. of dihydrostreptomycin for 4 days subsequently. In the suspected or frankly infected cases the use of antibiotics should be started before the operation and followed by the above-mentioned routine. With the routine use of these measures, the results of treatment of puerperal infections after cesarean sections have been more definitive and encouraging. The article is illustrated with many tables and a large number of references through the text.

RICARDO L. GORBEA

Carbone, Ralph, and Keating, William: Cesarean Section Report for 1951, Bull. Margaret Hague Maternity Hosp. 6: March, 1953.

In 1951, 315 cesarean sections were done at the Margaret Hague Hospital. This was an incidence of 3.6 per cent. In private patients the incidence was 3.9 per cent while in clinic patients it was 3.1 per cent.

The types of operation included 192, or 61 per cent, laparotrachelotomies, 119, or 38 per cent, extraperitoneal sections, and 3, or 1 per cent, cesarean hysterectomies. No classical operations were done. There was no maternal mortality.

Of 176 patients who had had previous cesarean sections, 96 had repeat sections, while 80, or 95 per cent, were delivered vaginally.

The perinatal mortality was 6.2 per cent, with 7 infants stillborn and 13 who died in the neonatal period, most of the latter being premature infants. In mature infants, the total mortality was only 1.4 per cent.

The chief indication was dystocia from various causes. The second most frequent indication was hemorrhage (44, or 14.0 per cent, of the group) due to placenta previa or abruptio placentae.

The third most frequent indication was toxemia of pregnancy (31, or 9.9 per cent, of the total sections).

Miscellaneous indications included 8 cases of fetal distress, 3 of maternal diabetes, 7 of prolapsed cord.

Conduction anesthesia was usually employed, spinal anesthesia alone in 163 cases and spinal with various supplements in 140.

Complications included hemorrhage in 12.4 per cent, shock in 2.5 per cent, bladder injury in 4 cases.

KARL M. WILSON

Litchfield, Harry R., Sternberg, S. David, Halperin, Jacob, and Turin, Richard: Fetal Mortality in Cesarean Section, J. A. M. A. 151: 783, 1953.

The authors report 969 cesarean sections performed at the Beth-El Hospital from 1945 to 1951, inclusive. These sections were done by various members of the attending and house staffs. There were a total of 44 fetal and neonatal deaths, giving a gross mortality of 4.5 per cent. Among the 44 infants who died, 3 were considered nonviable at the time of section, 11 were stillborn (all in the viable stage), and 25 were associated with either placenta previa or ablatio placentae. There were only 5 fetal deaths in patients who had elective sections prior to the onset of labor. In those infants on whom postmortem examinations were done pulmonary atelectasis, aspiration pneumonia, and hyaline membrane were the commonest findings. The authors feel that the reduction in the fetal mortality resulting from section for placenta previa was due to more conservative care of the patients presenting this complication. They are transfused repeatedly until the fetus becomes more mature and are kept under absolute bed rest. The authors call attention to the following points in their routine of cesarean section: (1) slow release of amniotic fluid when the uterus is opened; (2) after delivery placing of the infant below the level of the mother's abdomen, which allows blood from the placenta to run into the circulation of the infant; (3) general suction of the oral pharynx and nasal passages; (4) laryngoscopic intratracheal suction or oxygen insufflation when necessary; (5) aspiration of gastric contents; (6) placing of infant in a heated incubator in Trendelenburg position at an angle of 10 degrees; (7) transporting of infant to nursery in incubator.

WILLIAM BERMAN

Endocrinology

Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. 247: 829, 1952.

A clinical evaluation of Vallestril, a new synthetic estrogen related to allenolic acid, was made. The drug was administered orally to 28 women with severe menopausal

symptoms, 1 young woman with acne vulgaris, 3 women with postmenopausal osteoporosis, and 1 elderly man with prostatic cancer with osseous metastases.

An excellent result was shown by 12 of the menopausal women. Eight of the others had a good response, 5 had some improvement, and 3 had no relief. The drug did not produce uterine bleeding and was effective in all cases of postmenopausal osteoporosis. The 18-year-old girl with acne also showed improvement without menorrhagia. It was effective in the male patient with prostatic carcinoma without the development of gynecomastia, which had been troublesome while he was taking stilbestrol. Daily doses of 4.5 or 6.0 mg. produced results in most patients within three or four days of the initiation of therapy. One patient became nauseated on 7.5 mg. daily of the drug, but no other evidence of toxicity or withdrawal bleeding was encountered. Vaginal cornification was produced by the drug, but no consistent correlations were observed between dosage and degree of cornification or clinical improvement and cornification of the vaginal epithelium. The uptake of radioactive iodine by the thyroid gland was not changed in 2 patients who were taking therapeutic doses of Vallestril.

The authors felt that the drug compared favorably with other estrogens and seemed superior to most because of its lack of side effects, particularly the lack of uterine bleeding on withdrawal.

IRVING L. FRANK

Fluhmann, C. Frederic: Some Endocrine Effects of Neostigmine, Western J. Surg. **61:** March, 1953.

The cholinergic drug neostigmine, widely known under its trade name Prostigmine, is commonly used by the profession as a presumptive test for pregnancy. Daily injections of Prostigmine over a period of three days are generally thought to induce endometrial bleeding in nongravid patients within seventy-two hours after the last injection. No bleeding occurs if pregnancy is present. The induction of uterine bleeding has been thought to depend exclusively upon the cholinergic action of the drug, through its ability to neutralize the cholinesterase in the endometrium thus permitting acetylcholine to act upon the vascular bed to induce a hyperemia which is followed by bleeding. It is now suggested that this effect is not entirely local but may be mediated through a pituitary-ovarian stimulating effect of the neostigmine.

It is well known that the hypothesis is stimulated to activity through a reciprocal relationship which it has with its target glands. A fall in estrogen production is followed by an increase in gonadotropic secretion from the anterior pituitary. Adrenal-cortical failure is followed by increased output of ACTH from the anterior pituitary. It is also well known that the pituitary can be activated by neural impulses from the hypothalamus. Evidence is now presented to suggest that the cholinergic action of neostigmine may activate the pituitary in the rat. On the basis of the experiments which the author reported, it would appear that the daily injections of neostigmine over a period of some days to the 21-day-old rat is followed by evidence of ovarian activity resulting in precocious development of normal ovarian function and early opening of the vaginal introitus. Continued administration is followed by depression of ovarian function but this is soon followed by the establishment of normal ovarian activity with rhythmical estrous cycles.

In some respects the administration of neostigmine and estrogen is comparable in that both tend to increase the amount of available acetylcholine in the endometrium. Small doses of estrogen apparently favor ovulation through activation of the luteinizing hormone from the anterior pituitary and in like manner neostigmine may activate the anterior pituitary to produce the luteinizing hormone.

It must, therefore, be concluded that secretion from the endocrine glands is under a dual control, namely, neural and humoral.

WILLIAM BICKERS

Husslein, H., and Gitsch, E.: Upon the Thermogenetic Effect of Progesterone, Wien. Klin. Wchnschr. 64: 899, 1952.

Of all the steroid hormones, only the corpus luteum hormone normally raises the body temperature by about 5/10 degree centigrade. It has been pointed out that the thyroid or the diencephalon may also produce this effect. Ehlert observed in 5 women with secondary amenorrhea that when given 0.3 Gm. Luminal daily together with 10 mg. progesterone twice a day no elevation of the basic temperature took place, contrary to a typical rise before and after when progesterone alone was being administered. In a preliminary experiment with 22 women, 16 with amenorrhea and 6 with bleeding from cystic hyperplasia, the authors could not verify beyond doubt Ehlert's data. A second experiment with a group of 14 women, 7 of whom were given progesterone and Luminal, and 7 progesterone and Pyramidon did not give convincing results either. The authors feel that a positive thermogenetic effect depends on the amount of progesterone administered and the existing degree of estrogen concentration. Follicular hormone and progesterone are antagonistic concerning this influence upon the temperature center. But it is easier to produce a rise of temperature by progesterone during the physiological follicular phase than to lower the temperature by follicular hormone during the luteal phase. The body temperature is regulated by the diencephalon. Low temperatures go with parasympathetic, elevated ones with sympathetic preponderance. The term "follicular and luteal phase" might be replaced by "parasympathetic and sympathetic reaction." Thus the cycle is divided into a parasympathetic and a sympathetic phase. The first phase shifts into the second at the moment of ovulation or at the beginning of the progesterone synthesis. Moreover, during the follicular phase, phenomena occur which point to a parasympathetic preponderance and vice versa during the luteal phase. If the problem is approached from the vegetative viewpoint the thermogenetic effect of progesterone can be better understood. Its effects upon the vegetative nervous system provoke a condition of sympathetic reaction which promotes the preparation and maintenance of pregnancy.

C. J. EHRENBERG

Gynecology

Dedman, Harold E.: Routine Use of Pubocervical Fascia in Uterine Suspensions, Western J. Surg. 61: March, 1953.

The most satisfactory operations for uterine suspension depend upon a supporting fascial plane rather than the strictly suspending structures of the uterus such as the broad and round ligaments. The pubocervical fascia layer of the endopelvic fascia is a structure commonly used for the repair of the cystocele. Advancement of the bladder and suture of the pubocervical fascia high on the anterior wall of the uterus serve to correct the cystocele and at the same time to place an anterior pull on the uterine fundus at a higher level and thus hold the uterus in anteversion. In the absence of cystocele, retroversions of the uterus can be satisfactorily and permanently corrected by the same operation. In the case of intrapelvic disease where the abdominal cavity must be opened, a technique is described for utilizing the same pubocervical fascia in uterine suspension.

A transverse incision is made in the peritoneum at the uterovesical junction in the same manner as if one were to perform a hysterectomy. The bladder is dissected down and the peritoneum over the anterior wall of the uterus dissected up. The pubocervical fascia over the anterior wall of the vagina is exposed and a heavy mattress chronic suture passed through the pubocervical fascia posterior to the anteriorly retracted bladder and the same suture passed in mattress fashion through the raw surface at the upper angle of the peritoneeal reflection on the uterine fundus. Another mattress chromic suture is then placed at a point higher in the pubocervical fascia overlying the vagina and passed through the anterior wall of the fundus at a point just below the previous suture. When these two mattress sutures are tied, the pubocervical fascia is fixed to the anterior wall

of the uterus and the fundus brought well up behind the symphysis. The peritoneum is closed at the uterovesical junction thus extraperitonizing the operative site.

The author has performed this operation on 41 patients and in a rather careful follow-up study has been able to learn of only one patient in whom the uterus was subsequently found in retroversion. Results on the basis of anatomical findings and relief of symptoms suggest this procedure worthy of consideration.

WILLIAM BICKERS

Ruiz, M. Urrutia: Progress of Surgery on the Female Gonad, Ginec. y obst. de México 7: 393, 1952.

In an extensive and meticulously written article, the author brings forth all the fallacies and tragic results of unnecessary surgery performed on the ovary. He reviews the statistics of his own clinic and the world in general and enumerates the various procedures performed on the ovary, emphasizing the fact that surgery of the ovary should remain whenever possible conservative in nature. The fact that the morbidity and mortality of operative cases have diminished in later years makes the author formulate certain factors which he feels are responsible for this surgical pseudo-Utopia. They are as follows: (1) closer study and better preoperative preparation, (2) better control of asepsis, (3) safer anesthesia, (4) more exact surgical techniques, (5) appropriate use of sutures, (6) definitive hemostasis, (7) better postoperative care, (8) adequate control of dehydration, (9) restoration of electrolyte and protein balance, (10) more and better use of blood transfusions, (11) early ambulation and active mobilization, and (12) judicious use of all antibiotics and sulfonamides.

The author concludes his article with the following recommendations and conclusions: (a) necessity of complete preoperative study previous to surgical intervention, (b) the use of antibiotics which has diminished surgical indications, (c) endocrine and physiotherapy to avoid unnecessary operations, (d) more definitive and better-applied surgical techniques, (e) attempt by modern gynecological surgery to conserve normal tissues and preserve normal function or ameliorate it when it is found to be altered, (f) a plea for conservation of the ovary whenever possible, and (g) less unnecessary surgery of the ovary, which, when indicated, should be done properly.

This article is illustrated with many tables, and contains a bibliography of 110 references.

RICARDO L. GORBEA

Arzac, J. P.: Colpocytology in the Determination of the Ovulation Period in the Female, Estudios sobre esterilidad 3: 175, 1952.

The author in this article tries to correlate the basal body temperature curve phenomenon to the cytologic changes in the vaginal smear, in determining the ovulation period. He brings forth the limitations of the former method and the decided advantages of the latter. He is of the opinion that the cytologic study of the menstrual cycle gives us a more definitive answer. The study was based on 22 cases investigated, and it was found that in only 9 cases were both the basal temperature curve and the cytologic studies in absolute accordance. The clinical history of a case is fully presented involving a seven-year period of study, registering data for three planned pregnancies (delivered at full term) and coitus occurring during the so-called "safe period." The author divides the ovulation period into four distinct levels: ((1) period of fecundity, (3) period of potential fecundity, and (4) period of anticonceptional security.

The article is illustrated with four tables that show graphically the advantages of cytologic smear over basal temperature curve in determining the different periods of fecundity in women.

RICARDO L. GORBEA

McIntyre, J. P., Drimmie, Alison M. T., and Gordon, W. J.: Congenital Tuberculosis, J. Obst. & Gynaec. Brit. Emp. 60: 119, 1953.

The case of a 26-year-old patient who was found to have miliary tuberculosis in the fourteenth week of gestation is reported. She was treated with 0.5 Gm. streptomycin twice a day and para-aminosalicylic acid, 12 Gm. orally (3 Gm. four times a day) but signed herself out of the hospital against advice after 12 weeks. Two weeks later, in the twenty-eighth week of gestation, she developed tuberculous meningitis and 100 mg. dihydrostreptomycin was given intrathecally and 1 Gm. streptomycin intramuscularly daily. The patient's condition deteriorated and she died in 48 hours. Shortly before death labor began and she was delivered spontaneously of a premature child who succumbed shortly thereafter. Two minutes after the birth of the infant the placenta was delivered spontaneously. Autopsy on the mother confirmed the presence of miliary tuberculosis and tuberculous meningitis. The fetus weighed 655 grams and showed no evidence of tuberculosis on serial section of both the abdominal organs and the lungs. Death was attributed to prematurity and atelectasis, and as one of the contributory factors the total amount of streptomycin the patient received, 82 grams intramuscularly, is mentioned as perhaps not being entirely innocuous to the fetus. Examination of the placenta revealed numerous tubercles throughout its substance.

The author concludes that the placenta can provide an effective barrier against tuberculosis even in the presence of overwhelming disease in the mother. However, this is not always the case, as shown by the fact that ulcerative lesions can develop in the placenta. The author suggests certain measures to prevent a similar catastrophe, such as routine antenatal x-rays, admission of the pregnant patients to hospitals early for appropriate treatment of the chest condition, and avoidance of the routine practice of milking the umbilical cord in the tuberculous patient. He states that in some cases elective cesarean section after the twenty-eighth week should be considered. Probable modes of development of tuberculous disease in the fetus are discussed.

GEORGE SCHAEFER

Gynecologic Operations

Couri, A. A.: Treatment of Urogenital Fistulas, An. brasil. de ginec. 17: 25, 1952.

The author reports on a series of 36 urogenital fistulas treated during the last seven years at the Gynecological Institute of the University of Brazil. He stresses the importance of exact preoperative care and preparation, and recommends a simple technique of suturing which he used in the last eight cases, without in any way affecting the end results. Early ambulation and a tendency to avoid or shorten postoperative catheterization are features of this technique. The author stresses the importance of always trying the plastic procedure first and of repeating the plastic procedure in unsuccessful cases as many times as the surgeon sees progressive diminution of the fistulous opening, before performing exclusion of the bladder. These 36 cases were broken down by the author as follows: operated upon once, 25 patients; operated upon twice, 7 patients; operated upon 3 times, 2 patients; and operated upon 4 times, 2 patients. There were 51 operations performed in the following manner: (1) fistulectomy, vaginal approach, 36 cases; the transvesical, 4 cases; Ward's operation, 2 cases; Aldridge's operation, 3 cases; ureterocystostomy, 5 cases; and ureteroenterostomy (Davallos), 3 cases.

The causal factors for the fistulas were found to be (1) obstetrical, in 23 cases, 63.8 per cent; (2) surgical, in 10 cases, 27.7 per cent; and (3) inflammatory in 3 cases, 8.3 per cent. The operations were successful in 26 cases and unsuccessful in 10 cases.

RICARDO L. GORBEA

Conill, Victor: Ambulatory Colpoepisiocleisis for Senile Prolapse, Rev. mex. de cir., ginec. y cancer 20: 268, 1952.

The author introduces his article by making reference to all the known types of operations for correction of uterine prolapse in elderly women. He mentions the procedures

of LeFort, Lambhardt, Kahn, and Wahl. He stresses the number of days necessary for the patient to stay in bed, thus inviting complications. The author describes an operation which he devised and which, in his hands, apparently is the ideal procedure for treatment of uterine prolapse in older women. This procedure has been done in over 100 cases with no mortality and no recurrence of the prolapse. This new method is fundamentally an episiocleisis in which the colpocele sutures are incorporated in the vulvar sutures to prevent them from sliding down. The operation is done under local anesthesia and requires no rest. The patient is encouraged to go about her daily chores as usual, sitting at the table with the rest of the family and doing all other routines as before the operation. The scar attains a tendinous thickness of about 2 cm. Postoperatively the patient is given an enema and a course of antibiotics is started to prevent possible infection and dehiscence of the wound.

Under local anesthesia of 1.0 per cent Novocain, usually not more than 10 c.c. a square of vaginal mucosa over both colpoceles is excised. The margins of these are brought together with interrupted chromic sutures. Elliptical raw areas on both labia majora extending from just below the level of the urethra to the navicular fossa are excised. The inner margin of these areas are sutured to the outer margin of the excised vaginal squares with interrupted choromic sutures. The entire raw area is closed with through-and-through nylon sutures, approximating the raw areas in the midline just as in repairing a proctocele. Usually five sutures are required to close the denuded area. These sutures are removed in 10 days. The article is illustrated with 7 drawings that explain the procedure graphically.

RICARDO L. GORBEA

Pereira, P. B.: Hysterectomy in the Treatment of Benign Lesions of the Uterus, Rev. brasil. de cir. **24**: 327, 1952.

The author presents in this article a review of the literature as well as his own personal opinions on the advantages and relative limitations of the supravaginal hysterectomy and total hysterectomy through the vaginal or abdominal route, in the treatment of benign lesions of the uterus. He delegates the supravaginal hysterectomy as an operation to be used only in the exceptional cases because of its less difficult technique and where the cervix is above suspicion. In passing, the author analyzes the technical problems related to both the abdominal and vaginal approach, and defines the operative indications for each of the three procedures, supravaginal, total abdominal, and vaginal procedures.

In conclusion he brings forth the advantages of the vaginal approach when feasible, considering it the ideal method. He feels that by the vaginal approach we attain a smoother convalescense, less stormy postoperative period, absence of abdominal scar and consequently no possibility of incisional hernia, and a low index of morbidity and mortality.

RICARDO L. GORBEA

Newborn

Hsia, David Yi-Yung, Allen, Fred H., Jr., Diamond, Louis K., and Gellis, Sydney S.: Serum Bilirubin Levels in the Newborn Infant, J. Pediat. **42**: 277, 1953.

This study was undertaken for the purpose of obtaining data regarding the range of cord serum bilirubin levels and the range of daily bilirubin levels in full-term and premature infants and in infants suffering with erythroblastosis fetalis. These observations were made on infants seen at the Beth Israel, the Boston Lying-in hospitals, and Children's Medical Center, Boston.

This work again confirms the fact that an increase of serum bilirubin occurs in the first one or two days of life and that physiologic hyperbilirubinemia is not caused by blood group incompatibility. The prolonged elevation of bilirubin in premature compatible infants confirms the clinical impression that jaundice occurs more frequently and is more severe in prematures than in full-term babies, a fact no doubt related to the functional immaturity of the premature infant's liver.

In erythroblastosis there is added to the normal inability of the infant to dispose of bilirubin an increased rate of blood destruction, and, as a result, large amounts of bilirubin accumulate. Exchange transfusion, therefore, helps such infants materially in clearing their bilirubin. A level of serum bilirubin above 10 mg. per cent during the first 24 hours of life or the appearance of jaundice during this time should be considered to be due to erythroblastosis until proved otherwise. Serum bilirubin levels during the first two days of life, therefore, are of great diagnostic value as regards the existence of erythroblastosis, particularly in cases caused by ABO incompatibility. Furthermore, they are of considerable value as a guide to the therapeutic use of replacement transfusion.

HARVEY B. MATTHEWS

Hsia, David Yi-Yung, Allen, Fred H., Jr., Gellis, Sydney S., and Diamond, Louis K.: Erythroblastosis Fetalis. VIII. Studies of Serum Bilirubin in Relation to Kernicterus, New England J. Med. 247: 668, 1952.

Studies of serum bilirubin in relation to kernicterus were made in 229 infants with erythroblastosis fetalis. An effort was made to show a correlation between high serum bilirubin levels and the occurrence of kernicterus.

Although the data are probably biased in the direction of low bilirubin values because few maximum levels were obtained, the figures show that almost all the cases of kernicterus occurred in the infants with high bilirubin levels in each age group. In the cases in which the range was 0 to 5 mg. per 100 c.c., there was no kernicterus; in those in which the range was 6 to 15 mg., values were obtained in infants whose only bilirubin determination was in the first two hours of life. The levels undoubtedly rose much higher in the next forty-eight hours. Kernicterus occurred in 18 per cent of infants whose serum bilirubin was recorded at a level between 16 and 30 mg. per 100 c.c. and in 50 per cent of those in whom levels rose above 30 mg. per 100 c.c.

Therefore, although it has not been proved that bilirubin is the actual cause of brain damage, tests of serum bilirubin in babies with erythroblastosis fetalis serve as extremely valuable guides to treatment. The authors feel that kernicterus is likely to occur in babies with serum bilirubin levels above 30 mg. per 100 c.c. and unlikely to occur when the serum bilirubin remains below 20 mg. per 100 c.c.

By exchange transfusions, repeated if necessary, the serum bilirubin can be kept at relatively low levels, and kernicterus can be prevented.

IRVING L. FRANK

Lippsett, Shirley M., Bloch, Harry, Miller, Israel, Stein, Felix, and Lippsett, Herbert M.: Immunization of Newborn Infants With Pertussis Vaccine, J. Pediat. 42: 301, 1953.

The authors give a very short and comprehensive review of the subject of immunization of newborn infants with pertussis vaccine.

Their study consisted of a series of 117 infants divided into two groups: (1) a group that was given saline pertussis vaccine containing 20 billion organisms per cubic centimeter, in dosage of 1, 1.5, and 1.5 c.c. Total dosage was 80 billion organisms. At 9 months of age a 1 c.c. booster was given. The second group of infants received a specially prepared soluble detoxified alum-precipitated pertussis vaccine containing 40 billion organisms per cubic centimeter, in dosage of 0.5, 0.75, and 0.75 c.c. for a total of 80 billion organisms. These cases had a booster of 0.5 c.c. at 9 months of age.

There were only a few reactions to these injections which, when they did occur, were of a mild nature, such as moderate elevation of temperature, irritability, and mild local reactions.

The authors summarize the results of their work as follows: (1) newborn infants are particularly devoid of any pertussis antibodies; (2) injections of saline pertussis vaccine given to 22 newborns of 4, 8, and 12 weeks of age produced satisfactory pertussis agglutination in 13 (58 per cent) (although the titers were not high they were considered ade-

quate); and (3) injections of soluble detoxified alum-precipitated vaccine given to 22 newborn babies at 4, 8, and 12 weeks of age produced satisfactory immunization in all babies. Titers were high in 90 per cent.

HARRY B. MATTHEWS

Pregnancy Complications

Dewhurst, C. J.: Kyphoscoliosis Complicating Pregnancy, J. Obst. & Gynaec. Brit. Emp. 60: 76, 1953.

The author briefly describes nine vaginal deliveries in four cases of kyphoscoliosis complicating pregnancy. One patient died of heart failure with a dissection aneurysm of the aorta. Two patients had hypertensive complications. The babies were smaller than average size, and all were alive and well.

Kyphoscoliosis is discussed from the standpoint of the obstetric and the cardiorespiratory problems. The exact nature of the pelvic changes and the obstetric problem depend upon the situation of the spinal deformity. Lumbar involvement tends to reduce the pelvic inclination, increase the anteroposterior diameter and narrow the outlet. The addition of scoliosis may also produce obliquity of the pelvis. These pelvic deformities increase the incidence of dystocia. Nevertheless, even in the most unlikely cases where there may be pelvic deformity, dwarfism, pendulous abdomen, or even moderate outlet contraction, vaginal delivery may occur with surprising ease.

Marked kyphoscoliosis with dorsal deformity presents a very real danger of cardiorespiratory complications. There is strain on both sides of the heart. Pulmonary compression leads to the formation of areas of atelectasis and emphysema. Respiratory exchange is inefficient and vital capacity is reduced. These changes are aggravated by the additional burden of pregnancy. Special cardiac evaluation is indicated in the kyphoscoliotic patient contemplating marriage or pregnancy. The presence of dyspnea, cyanosis, or severe thoracic deformity with a low vital capacity may be sufficient to make advisable a warning against the additional burden of pregnancy.

CURTIS MENDELSON

Zapatero, J.: Pulmonary Tuberculosis and Pregnancy, Toko-Ginec. práct. 12: 80, 1953.

This study considers the evolution of the treatment of tuberculosis in its relation to coexistent pregnancy. The author starts with a reference to the thoughts of the days of Hippocrates when it was common practice to advise the tuberculous patient to marry and become pregnant as a means of controlling the disease. Such advice was prevalent until the nineteenth century when Grisolle in 1850 published a paper on the detrimental effect of pregnancy in a series of cases observed by him. After this it was the trend then to interrupt pregnancy in tubercular patients. It was not until the work of Brauning was published that the trend changed. This occurred in 1935 when Brauning expounded the idea that pregnancy did not aggravate tuberculosis and advised against interruption of pregnancy since it was injurious to the patient. In Europe as well as here in America this has since been the prevalent school of thought. Treat the tuberculous condition and disregard the presence of pregnancy. The author evaluates the treatment of tuberculosis, making note of the new antibiotics as well as the recently discovered drugs, streptomycin, paraaminosalicylic acid, and the hydrazine compounds. If indicated, interruption should be done preferably before the third month. There are many bibliographical references throughout the text.

RICARDO L. GORBEA

Glasser, John A.: Hemorrhoidectomy at the Time of Delivery, Bull. Margaret Hague Maternity Hosp. 6: March, 1953.

The author recommends the removal of painful thrombosed hemorrhoids during the pregnancy or immediately following delivery.

In 59 women such operation was carried out, 3 during pregnancy, 4 several days post partum, and 52 at the time of delivery. The results were extremely satisfactory with no complications developing, and eliminating the great discomfort which these thrombosed hemorrhoids can cause the obstetrical patient.

KARL M. WILSON

FitzGerald, T. B.: Angular Pregnancy, J. Obst. & Gynaec. Brit. Emp. 59: 518, 1952.

This case report has to do with a case of pregnancy in a septate uterus that was operated upon at the sixteenth week of pregnancy for continued severe pain in the lower right side, vaginal bleeding, and a "tumor in the lower pelvis apparently situated to the right of the uterus." At operation, due to the configuration of the uterus and the past history, the diagnosis was changed to angular pregnancy. Nothing was done because the asymmetry of the pregnant uterus was the only abnormality found. Convalescence was smooth and the pregnancy continued, under almost constant observation, for seven days past the estimated due date. Medical induction of labor was begun and with the last dose of Pitocin the fetal heartbeat became irregular. After three hours of observation, with increased irregularity and slowing of the fetal heart tones, a low segment cesarean section was performed and a living child delivered by the breech without mishap. Upon examination of the uterus it was found to be divided into two unequal compartments by a well-formed septum extending from the fundus to the lower segment. The child and the placenta occupied the right compartment of the uterus which corresponded with the operative findings at the sixteenth week of gestation. Convalescence was uneventful. Because of the change in diagnosis together with the author's great interest in angular pregnancy, he paradoxically chose to discuss the general subject of this condition rather than that of congenital malformations of the uterus and pregnancy as the case herein reported illustrates.

Angular or cornual pregnancy is not uncommon. The "lopsided" pregnant uterus that is not infrequently encountered on pelvic examination in the early months of pregnancy is usually due to the implantation of the ovum in the angle of the uterine cornu and has been designated as angular pregnancy, sometimes, and especially in America, called cornual pregnancy. In such cases the pregnant uterus assumes its normal shape by the twelfth to fourteenth week of gestation when the conceptus should fill the uterine cavity. However, when the asymmetry of the pregnant uterus continues beyond this period of gestation and up to term pregnancy a true congenital malformation is present. There are many types of malformed uteri; some malformations are moderate and offer no hazards to the pregnancy or delivery while others are extreme and cause all kinds of complications during pregnancy, at delivery, and during the postpartum period.

The author's conclusions are as follows: (1) Angular pregnancy is a real clinical entity. It occurs in early pregnancy and may be a potent cause of abortion. (2) Considerable confusion has arisen in connection with this condition because of the inclusion of cases of congenital malformations of moderate degree. The symptoms and signs in early pregnancy are much the same, consisting of pain, vaginal bleeding, and asymmetrical enlargement of the uterus. (3) The diagnosis of congenital malformation may be made when the asymmetry of the uterus persists beyond the fourteenth to sixteenth week of pregnancy and up to full term. It should be kept in mind that the degree of asymmetry depends upon the degree of malformation, the stage of gestation, and the location of the placenta.

HARVEY B. MATTHEWS.

Hosemann, H.: Prolonged Pregnancy, Zentralbl. f. Gynäk. **74:** 1441, 1952.

The question of prolonged pregnancy, as dated from the time of the last menstrual period, is raised, together with the effects of such prolongation of gravidity upon the size, weight, and health of the baby. In women whose menstrual history shows a 28 day cycle, the author feels that if gestation exceeds 290 days, as dated from the last menses, the

pregnancy is overmature. As far as the baby is concerned, the author states that, on a statistical basis, as many small children are delivered as are babies that are considered to be above normal in weight and size. Furthermore, on the basis of the same statistical studies, he notes that no untoward result can obtain if the fetus remains in the uterus for a longer period of time. The increased duration of pregnancy is not caused by the developing fetus but is entirely controlled by the physiological processes of the mother. The size, height, or weight of the mother similarly is not important in limiting the duration of pregnancy in that both fat and lean women carry sometimes longer than expected.

The author has studied the menstrual histories and pregnancy duration in 33,000 deliveries. In this entire series there were only 141 women who could definitely be proved to have exceeded the normal duration of 290 days. Of these, 44, or 36 per cent, carried two or more pregnancies for approximately the same period of time. The author has also examined the familial histories of these women and states that he feels there is a definite inherited factor.

Although he states that the increase in intrauterine residency in itself has no deleterious effect on the fetus, in those cases where the fetus is larger than normal, the trauma of delivery, plus possible senile degeneration of the placenta, could possibly increase fetal mortality. Therefore, if these factors can be demonstrated, labor should be induced at the expected time or shortly thereafter.

L. B. WINKELSTEIN.

Bowers, D.: Mumps During Pregnancy, West. J. Surg. 61: 72, 1953.

Interest in the relationship between virus infections during the first trimester of pregnancy and congenital defects has been rather well established. These defects are known to follow particularly in the wake of rubella. The effect of mumps upon the fetus during the first trimester is not well documented. The author reports two cases.

The first patient was a woman, aged 21 years, who had had two living healthy children and one spontaneous abortion. In the fifth week of her fourth pregnancy she developed bilateral parotitis, crampy low abdominal pain, and vaginal bleeding. Two days later she expelled a macerated fetus. The following day meningoencephalitic symptoms developed and the diagnosis of mumps-encephalitis was confirmed.

The second patient was a woman, aged 31 years, with three healthy children, who in the tenth week of her fourth pregnancy sought advice for vaginal bleeding and abdominal cramps. Three days after the onset of these symptoms she developed bilateral mumps. The following day she expelled a normal-appearing male fetus of approximately ten weeks' gestation.

A study of the literature reveals 84 recorded cases of mumps complicating pregnancy and in this group there were nine pregnancies which terminated in fetal death and twelve in fetal injury. It is more than probable that fetal injury or death may result from mumps complicating pregnancy.

WILLIAM BICKERS.

Weiner, W., Norris, V., and Davidson, S.: Transfusion Treatment of Women of Childbearing Age, Brit. M. J. 2: 975, 1952.

Among the mothers who produced children affected with hemolytic disease are those whose immunization was caused or stimulated by previous transfusions of Rh-positive blood. This study was undertaken to determine whether the number of patients immunized by transfusion therapy in the past has declined lately. For this purpose the records of 82,000 patients whose blood samples had been tested by the Regional Transfusion Service, Birmingham, were investigated. The study encompasses the period of 1940 to 1949, with the dividing line, December, 1947, chosen because knowledge of the dangers of nonhomologous transfusions became widespread and the supply of Rh-negative blood was somewhat plentiful.

There were 13,169 patients found to be Rh negative and of these 515 were immunized. Also, of the over 13,000 Rh-negative patients, 243 gave a history of having had blood transfusions or blood injections at some time during life. Of these 243 patients, 87 were immunized.

It was found that over 40 per cent of Rh-negative individuals transfused prior to 1947 were immunized. This percentage declined to 30 in 1947, 27 in 1948, and 11 in 1949. The over-all figure for the years 1940-1947 was 41.7 per cent versus 20.6 per cent for the years 1948-1949. It is quite evident that after 1947 the number of immunized Rh-negative women was less, but, with or without transfusion, a certain number of the patients were bound to become immunized by bearing Rh-positive children. The authors reach the conclusion that no case of immunization by transfusion in a female should ever occur; that although figures for the final few years of this study show marked improvement there is no room for complacency. They feel that in the ordinary transfusion there is ample time to group and type patients so that homologous blood may be given. With regard to emergency transfusions they advise treating the patient as though she were Rh negative until proper grouping can be reported and homologous blood administered.

JOHN T. COLE.

Hamilton, Hugh G., Higgins, Robert S., and Alsop, Webb S., Jr.: Iron Metabolism in Anemias in Pregnancy, South. M. J. 46: 117, 1953.

The classification of the anemias in pregnancy suggested by the authors is as follows:

A. Anemias Directly Related to Pregnancy.—
1. Iron deficiency anemia in pregnancy
2. Megaloblastic anemia in pregnancy
3. Hypoplastic anemia in pregnancy

B. Anemias Not Directly Related to Pregnancy.—
1. Sickle-cell anemia
2. Hemolytic anemia
3. Cooley's anemia
4. Anemia of infection, etc.

A normal woman has a total iron value of about 4.0 Gm., about 700 mg. being stored in the liver, spleen, and bone marrow, and about 3,000 mg. in the hemoglobin. As pregnancy progresses the woman is subjected to a variety of iron losses. About 400 mg. is needed for additional hemoglobin synthesis in her ever-increasing blood volume. This reduces her iron storage to about 300 mg. She loses 1 mg. of iron per day by excretion in urine, feces, and perspiration. The average daily diet contains 7 to 12 mg. of available iron. Hence only about 200 mg. of iron can be expected from the normal diet in the course of her pregnancy. In the last trimester approximately 500 mg. of iron must be transferred across the placenta to the fetus for hemoglobin synthesis. At the time of delivery she will lose at least 100 mg. of iron in the placenta. If the blood loss at delivery is 150 to 250 c.c. she will again lose 100 mg. of her available iron. If the woman nurses her child she will lose an additional 1 mg. of iron per day in the breast milk. It is obvious that pregnancy induces iron deficiency in all women unless therapeutic steps are taken to replace the iron loss.

The great majority of pregnant women will absorb, utilize, and metabolize the ferrous salt of iron. However, there is a group, perhaps 25 per cent, in whom absorption must be aided by the administration of vitamin C and hydrochloric acid.

Megaloblastic anemia in pregnancy is reasonably rare. The diagnosis can be made only by bone-marrow studies. Remissions may be induced by the administration of vitamin B_{12}. Hypoplastic anemia responds neither to iron nor to other hematopoietic substances and can be properly managed only by repeated blood transfusion.

The authors summarize their report by saying that 74 per cent of all cases were successfully treated with oral iron alone. Ten per cent were successfully managed on

iron plus hydrochloric acid. Four per cent required intravenously administered iron, and 0.7 per cent of cases fell into the megaloblastic type which responded to folic acid therapy. In eleven cases hemoglobin values could not be maintained by any of these therapeutic methods.

Supplementary oral iron can be absorbed at a maximum rate of only 5 mg. per day and since the total deficit in pregnancy is about 700 mg., it is obvious that oral iron therapy should be instituted at least 150 days before the anticipated date of delivery.

WILLIAM BICKERS.

Sterility, Fertility, Contraception

Sharman, Albert: Endometrial Tuberculosis in Sterility, Fertil. & Steril. 3: 2, 1952.

The author emphasizes that unsuspected endometrial tuberculosis may be the cause of sterility in an apparently healthy young woman. This disease was found in over 5 per cent of patients with primary sterility subjected to curettage or biopsy in the wards or sterility clinic of the Royan Samaritan Hospital for Women, Glasgow. It is also believed that, due to elusive microscopic evidence, the true incidence is probably very much higher.

These patients are seemingly healthy and only a few have had any manifestations suggesting tuberculous origin of the endometritis, namely, pleurisy, enlarged abdominal glands, or peritonitis, and tuberculosis of the neck glands and spine.

Tubal insufflation reveals occlusion of the Fallopian tubes in about 70 per cent of the cases.

Endometrial tuberculosis is usually secondary to tubal infection and, for that reason, cure cannot be effected by curettage and restoration of fertility is highly improbable. This condition is known to persist after curettage, bilateral salpingectomy, or bilateral salpingectomy with fundectomy.

E. C. HUGHES.

Geiger, R.: "Gamete Allergy" and Sterility, Zentralbl. f. Gynäk. 74: 1932, 1952.

In recent years a new concept of "gamete" antagonism or "sperm-allergy" has been developed for those cases of human sterility in which no definite pathological or physiological factors could be found to explain the inability of fertilization. This theory has often been called into use to explain the sterility of couples in cases where the individuals remarry and have offspring with other partners. Up to now no specific experimental evidence has been produced to verify such a theory, the concept being based solely on empirical clinical findings. In the American literature such a situation was thought to exist, and the use of hyaluronidase exploited for its cure.

The author has tried experimentally to verify this concept. He has noted that there is a definite allergic response to intradermal injections of specific sperm. In sterile matings this response occurs with a much greater dilution of the sperm than in those couples in whom sterility is not a factor.

The following case with diagnosis and therapy is quoted. A 30-year-old woman had a child 9 years previously by a first husband. However, after 5 years of sterility with a second husband, intradermal testing for sensitivity with the husband's sperm (0.05 c.c. diluted to 1:1,000) gave a strongly positive response. Since a normal reaction does not occur with dilutions greater than 1:100, it was felt that a definite allergy against this particular sperm was present. Desensitization procedures by means of gradually increasing doses of sperm solutions were carried out over a period of four months, each injection being given one week apart until 0.5 c.c. sperm in 1:2 dilution gave a minimal reaction. The spermatoxin used for injection was made by addition of carbolic acid (1 drop in 5 c.c.) to the seminal fluid. Immediately subsequent to this, the woman became pregnant. Other cases where spontaneous abortion occurred were treated similarly when intradermal tests gave positive results. The author is unable to explain the cause or the reason for

such specific sperm antagonism, but he feels sure that the sterility of this type can be overcome by the method described above, which is identical to the methods used in desensitizing other allergies.

L. B. WINKELSTEIN.

Krogner, K.: The Relation of Conception to the Basal Temperature Curve, Zentralbl. f. Gynäk. **74**: 138, 1952.

The use of basal temperature curves in women for the determination of follicle rupture and the resultant corpus luteum phase is well known and frequently advised in cases of sterility today. It is a simple method and requires a minimum of special apparatus and time. Many workers have confirmed the existence of this relationship, experimentally, by visualization of the ovary at the time of ovulation by peritoneoscope or at laparotomy. The reason for this small but definite change in the basal temperature is not clearly understood, but it is thought that this rise, superimposed on the normal diurnal temperature variation, is a function of the corpus luteum, and actually mirrors the rise and fall of that hormone in the body. This paralleling of the basal temperature and the corpus luteum production is also demonstrated by the fall in temperature occurring just before menstruation as well as the maintenance of a high basal temperature during the first trimester of pregnancy.

However, the clinical results have not been so successful when the basal temperature has been used as a guide in the determination of the optimal time for coitus in cases of sterility. This is probably due to the fact that the rise in temperature itself was used as the indicator of ovulation. The author has produced evidence that this is not exactly true. On the basis of controlled cohabitation studies, correlated with basal temperature curves, the majority of pregnancies occurred when coitus was consummated two to three days before the rise in basal temperature occurred, as compared with those cases when coitus was performed at or after the temperature elevation. Basal temperature graphs in a series of cases where one cohabitation only was allowed during the "fertile" period amply demonstrate this fact.

The author theorizes as to two possible explanations for this. First, he states that the sperm must be at the site of fertilization at the time ovulation occurs, and that the time for the travel of the spermatozoa may be greater than was previously estimated. Second, and more probably, he feels that, since the temperature rise is a function of the corpus luteum, it will not occur until the corpus luteum becomes a true functioning organ, which cannot occur until the organization of the follicle is physiologically complete, and which cannot possibly be for a minimum of two or three days after the actual rupture of the ovum occurs.

L. B. WINKELSTEIN.

DoAmaral Ferreira, Clarice, Bittencourt, Lourdes, and Moreira, Avani: A Ten-Year Report on Sterility, Outpatient Department of the Institute of Gynecology at the University of Brazil, An. brasil. de ginec. **17**: 289, 1952.

A statistical report on the first ten years of activity of the Sterility Outpatient Department at the Institute of Gynecology of the University of Brazil is made by the authors. Tests and examinations carried out for investigation of underlying factors of sterility or infertility in 220 patients are described together with results of treatment. In this series 35 per cent of the patients gave up before investigation was finished, 31.5 per cent gave up after treatment was started, 13.5 per cent are still under treatment.

Out of the 20 per cent who followed the treatment subscribed, 8 became pregnant (20 per cent); 5 of whom went to term (12.5 per cent). The authors tabulate the apparent causes of sterility, primary or secondary, as well as the treatment indicated for each patient. They used every possible test available, basal metabolism, vaginal smears, Huhner test, salpingograms, sperm count, etc.

RICARDO L. GORBEA

Correspondence

About the Equipment for the Immediate and Complete Care of the Newborn

To the Editor:

In the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. 64, September, 1952, an article appeared by Bernard E. Cappe and Irving M. Pallin, titled "Receiving Crib for the Newborn," in which the above-mentioned authors propose a crib designed to facilitate the first care of the child.

Although this crib of the two colleagues of Brooklyn can be useful, we wish to refer to the one we presented at the Seventh Argentine Congress of Obstetrics and Gynecology held in Buenos Aires, on Oct. 26, 1949, and also at the Third Chilian Meeting of Obstetrics and Gynecology held in Santiago, Chile, on Dec. 7, 1949. These papers were published in *El Dia Médico*, 1950, pp. 548-549, and in the *Transactions* of the Chilian meeting, pp. 362-364, and in the *Annals of the Obstetrical Department of the Cosme Argerich Hospital*, 1949, vol. 3, pp. 34-39 and 40-43.

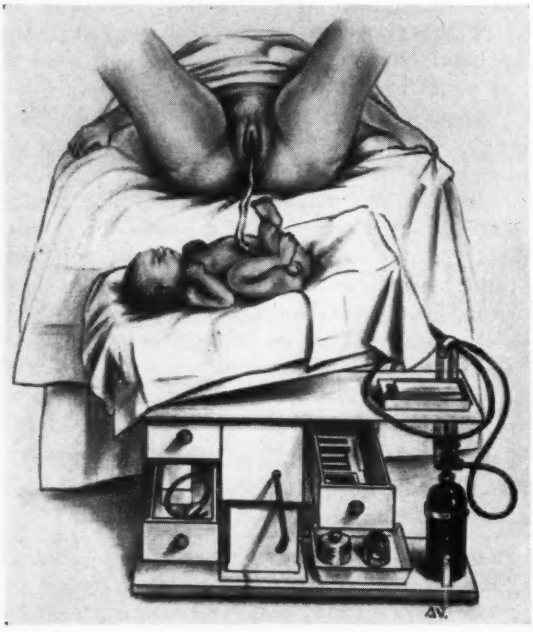

Fig. 1.—Receiving crib for the newborn in its relation to delivery table.

Our crib was also the subject of a paper titled "Our Procedure for the Immediate and Complete Care of the Newborn" at the International and Fourth American Congress on Obstetrics and Gynecology, held in New York, in May, 1950, which appeared in the TRANSACTIONS of this meeting, pp. 233-235.

We will not take time to describe once again our equipment, one illustration of which accompanies this letter.

Its advantages, to our minds, are:

A. It permits heating, thanks to electric lamps, to keep the child from catching cold.

B. It allows a greater quantity of blood from the placenta and from the cord to pass into the fetal circulation.

C. It facilitates the drainage of the upper respiratory tracts, as the child is placed in Trendelenburg position.

D. It simplifies all the care of the newborn (prophylaxis of the ophthalmia, aspiration of mucus, insufflation with the Graber equipment), because the table is provided with all the elements necessary for this. It is not, however, only because of a question of priority that we wish to refer to our table, but because of the superiority which it offers with its system of heating, its height and inclination which can be regulated, and all the resources which it has for the immediate attention.

JUAN LEÓN AND CARLOS T. LEÓN

DEPARTMENT OF OBSTETRICS
ARGERICH HOSPITAL, BUENOS AIRES, ARGENTINA.
APRIL 30, 1953.

Fluid and Electrolyte Distribution in Pre-eclampsia

To the Editors:

The research of Drs. Lambiotte-Escoffier, Moore, and Taylor into the fluid and electrolyte distribution in pre-eclampsia provides the data that there is an increased tissue content of water and of sodium in pre-eclampsia, while the extra-cellular fluid content is unaltered.

Reference is made to the work of Gaudino and Levitt[1] to explain the implied redistribution of water and sodium from extra-cellular to intra-cellular space, under the influence of Cortisone, ACTH, and DCA. Retention of sodium and water, when ascribed to corticoid influences, is held primarily to be due to DCA. In this connection I will quote Homer Smith[2]: "Gaudino and Levitt have re-examined the question, using isotopic Na^{24} and K^{42}, inulin as a measure of extra-cellular space, and D_2O as a measure of total body water. They find that the administration of DCA to two normal dogs led to expansion of the extracellular space (+40 to +53 per cent) at the expense of the intra-cellular space (-33 to -43 per cent), the intra-cellular concentrations of sodium and potassium being reciprocally elevated at the peak of the response. The filtration rate is increased . . . as did the renal plasma flow . . . serum potassium fell to nearly half its control value, plasma sodium remaining unchanged. Total body sodium increased by 30 per cent over a period of sixteen days, with a simultaneous increase in the average intra-cellular concentration of this ion." By accepting these findings, implied by their reference to them, it becomes difficult to envisage how the authors of your communication can reconcile them with the shift of fluid in the opposite direction which they state occurs in pre-eclampsia, and which is in accordance with further findings of Gaudino and Levitt when exhibiting adrenal corticoids, for their effects are diametrically opposed. The difficulty is augmented by the fact that Borst[3] has shown that increase of extra-cellular fluid is accompanied by a diuresis provided that renal and cardiac function are unimpaired—and the latter is not under suspicion in pre-eclampsia. In this view the expansion of the extracellular space would be remedied by such a mechanism if the renal function was within normal limits and there would be no increased total body water or sodium on which a shift from extra- to intra-cellular space could be based. Further doubt is thrown on the validity of their hypothesis by the work of Prunty[4] who finds that the adrenal corticoids increase the amount of the extracellular fluid at the expense of the fluid in the cells.

Prunty[4] further states, "Only recently have studies commenced to determine the effects on renal excretion of water and electrolytes in response to expansion of extracellular volume, a basic requirement in evaluating the response to cortical hormones. These observations stress the importance of posture and the diurnal variation in the responses

obtained. The increase in volume of this fluid seems to limit the water and electrolyte retaining properties of the adrenal hormones in the normal individual, the concentration of sodium in the fluid being a matter of secondary importance."

The article in your JOURNAL also fails to offer data of the potassium level in the plasma. The behaviour of this electrolyte has particular significance when corticoid mechanisms are claimed to underlie physiological or pathological phenomena.

According to Warren and Stead,[5] who administered sodium chloride to two oedema-forming patients, there is an accumulation of extra-cellular fluid to account for the increase in body weight. They inferred the site of this accumulation in the extra-cellular space because of an increase in the plasma volume. This evidence also is therefore contrary to the findings of Dr. Lambiotte-Escoffier.

Cox and Chalmers have shown that the average value of the sodium space is higher in pre-eclamptic toxaemia compared to normal pregnancy and as this space corresponds almost exactly to the extra-cellular space, it is to be inferred that in pre-eclamptic toxaemia the volume of the extra-cellular fluid is increased.

I feel that it would be unwise finally to accept the explanation of the data of your authors when so many intruding factors need assessment, especially as oedema is gravitationally manifested, thereby arguing against a lockup of fluid in cells.

JOHN SOPHIAN.

24 BAINES AVENUE
SALISBURY,
SOUTHERN RHODESIA

References

1. Gaudino, M., and Levitt, M. F.: J. Clin. Investigation 28: 1487, 1949.
2. Smith, Homer: The Kidney, New York, 1951, Oxford University Press, p. 360.
3. Borst, J. G. G.: Second International Congress of Internal Medicine, London, 1952, Abstracts, pp. 10, 11, 12.
4. Prunty, F. T. G.: Second International Congress of Internal Medicine, London, 1952, Abstracts, pp. 12, 13.
5. Warren, J. V., and Stead, E. A.: Arch. Int. Med. 73: 138, 1944.
6. Cox, L. W., and Chalmers, T. A.: J. Obst. & Gynaec. Brit. Emp. 60: 214, 1953.

In Memoriam

DR. LOUIS E. PHANEUF, gynecologist and teacher, long identified with the Carney Hospital of Boston, past President of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Fellow of the American Gynecological Society, and member of numerous specialist organizations, died on Sept. 20, 1953, in Boston, at the age of sixty-nine, following an operation for gastric ulcers.

Items

The American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States, Canada, and military centers outside the continental United States, on Friday, Feb. 5, 1954.

Case abstracts are to be sent by the candidate to the Secretary as soon as possible after receiving notification of eligibility to the Part I written examination.

Candidates are reminded at this time that Application for re-examination in Part II must be made by the candidate prior to February 1 of any year.

ROBERT L. FAULKNER, M.D., SECRETARY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

Fourteenth British Congress of Obstetrics and Gynaecology

The Fourteenth British Congress will be held at Oxford, July 27 to 30, 1955. Subjects already selected for discussion are:

1. The Role of the Qualified Midwife, the Family Practitioner, and the Obstetric Specialist in the Conduct of Normal Labour.
2. The Aetiology, Prevention, and Treatment of Pre-eclamptic Toxaemia of Pregnancy.

Gynaecological subjects will be announced later.

All communications relating to this Congress should be addressed to the Secretary, Fourteenth British Congress, Maternity Department, Radcliffe Infirmary, Oxford.

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AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD., ST. LOUIS 3, U. S. A.

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Vol. 66, No. 1, July, 1953. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its Possessions, Pan-American Countries, $15.00 a year; Foreign Countries, $16.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

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VOL. 66 DECEMBER, 1953 NO. 6

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD., ST. LOUIS 3, U. S. A.

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Vol. 66, No. 6, December, 1953. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its Possessions, Pan-American Countries, $15.00 a year; Foreign Countries, $16.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.